UPFRONT SURGICAL MANAGEMENT OF WILMS' TUMOR

Thesis
Submitted for partial fulfillment of MD degree in surgical oncology

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ABSTRACT

**Background:** Over the past decades, 2 different approaches for the treatment of Wilms tumor have emerged: upfront nephrectomy (UN) and preoperative chemotherapy (PC), with adjuvant treatment adjusted to stage, histology, and chemotherapy response. Data from the International Society of Pediatric Oncology (SIOP) suggested decreased intraoperative spillage and more feasible surgery after PC. The Children Oncology Group (COG) has adopted the concept of UN assuming the feasibility of the resectional surgery and the proper staging information that may be lost with the administration of PC.

**Methods:** Patients with unilateral renal masses diagnosed as WT who presented to the Children Cancer Hospital of Egypt (CCHE) from January 2009 to January 2012, were subjected to UN with the exclusion of those who are not amenable to this approach based on the proposed COG protocol, to be treated first by chemotherapy.

**Results:** One hundred seven patients were identified (35 PC and 72 UN). Preoperative chemotherapy had more incidences of surgical complications. Intestinal obstruction was the most common post operative complication. Event free survival and overall survival were 76.8% and 79.9% for PC at 30 months vs 87.5% and 95.8% for UN at 36 months.

**Conclusion:** Preoperative chemotherapy (PC) and Upfront nephrectomy (UN) are equally effective in the treatment of WT with no real difference in EFS. But we find a statistically significant OS in favour of the UN group. Upfront surgery has its advantages and limitations, in view of international as well as our series. UN approach can be effectively adopted in a developing country.

**Keywords:** Wilms' tumor, upfront Nephrectomy, complications.
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<td>COG</td>
<td>Children’s Oncology Group</td>
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<td>EFS</td>
<td>Event Free Survival</td>
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<td>FHWT</td>
<td>Favorable Histology Wilms’ Tumor</td>
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<td>IOS</td>
<td>Intraoperative Spillage</td>
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<td>MDT</td>
<td>Multi-disciplinary Team</td>
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<td>MIS</td>
<td>Minimally Invasive Surgery</td>
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<td>NSS</td>
<td>Nephron Sparing Surgery</td>
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<td>NWTS</td>
<td>National Wilms Tumor study</td>
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<td>OS</td>
<td>Overall Survival</td>
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<td>PC</td>
<td>Preoperative Chemotherapy</td>
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<td>SIOP</td>
<td>Societe Internationale d’ oncologie pediatrique</td>
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<td>UN</td>
<td>Upfront Nephrectomy</td>
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<td>UWT</td>
<td>Unilateral Wilm’s Tumor</td>
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INTRODUCTION
INTRODUCTION

- Wilms' tumor (WT) or nephroblastoma is the most common primary malignant renal tumor in children. In children under 15 years of age, the annual incidence rate of WT in USA is about 7-10 cases per million, and this accounts for 6-7% of all childhood cancers. (Smith M et al. 1998). More than 80% of cases are diagnosed before 5 years of age, with a median age of 3.5 years. (Breslow et al. 2006). A family history of WT is present in 1-2% of newly diagnosed patients, and has been localized to two familial WT genes (FWT1 at 17q12-q21 and FWT2 at 19q13.4). (Rutshouser et al. 2004).

- **Histology** is the most important prognostic indicator for WT. The majority of WT patients have tumors with favorable histology (FH). Several other unfavorable histological types are associated with an increased risk of tumor recurrence, or resistance to standard WT chemotherapy. Histological classification has been very important in stratifying patients into treatment groups and protocols. (KO EY, et al. 2009).

- **Stage** of the tumor is the second most important determinant of outcome in children with WT. There are currently two staging systems available reflecting treatment differences; the Children Oncology Group (COG) Wilms' tumor staging system and the International society of pediatric oncology (SIOP) staging system. The COG reflects staging at primary surgery. Alternatively, the SIOP is performed after preoperative chemotherapy. (Green et al. 1994).

- The improved imaging has now obviated the need for exploration of the contralateral kidney. (Ritchey et al. 2005). However, one limitation of imaging is the ability to determine resectability. So, surgical exploration remains the deciding tool for resectability. (KO EY, et al. 2009).
• Surgery maintains an important role in treatment, though the improved prognosis for this malignancy during the 20\textsuperscript{th} century is attributed primarily to advances in chemotherapy. (Metzgar et al. 2005).

• Transperitoneal radical nephrectomy is the standard operative procedure for unilateral WT. Although formal lymph node dissection is not needed, sampling of hilar and ipsilateral para-aortic or caval lymph nodes is mandatory. Determination of resectability should be based on findings at exploration. One exception is the diagnosis of extension into the IVC above the level of the hepatic veins. (Ritchey et al. 2005) (Shamberger et al. 2001).

• Surgical removal of a large renal mass in a small child has inherent risks. The most common intraoperative complications are tumor rupture and bleeding. Post-operatively, the most common complication is small bowel obstruction occurring in more than 5% of patients. Chylous ascites is a less common but significant event. The overall surgical complication rate of nephrectomy for WT appears to have declined over time. (Ritchey et al. 2001) (Ritchey et al. 2005)(Weiser et al. 2003)

• The dramatic increase in cure rate of Wilms’ tumor over the past 40 years is largely a testimony to the efforts of cooperative groups consisting of oncologists, surgeons, radiation oncologists, pathologists, and statisticians.

• Because of the relative rarity of this tumor, all patients with Wilms' tumor should be enrolled into a clinical trial. Treatment planning by a multidisciplinary team of cancer specialists (pediatric surgical oncologist, pediatric radiation oncologist, and pediatric oncologist) with experience in treating Wilms' tumor is required to determine and implement the optimum treatment. The National Wilms' tumor Study (NWTS) Group, which is now part of the Children’s Oncology Group, has established standard treatment for Wilms' tumor in North America which consists of
surgery followed by chemotherapy and, in some patients, radiation therapy (Green M 2004).

- More than 90% of patients are now expected to have excellent outcome with current treatment modalities. Contemporary issues involve stratifying children into low, intermediate and high risk categories, so as to reduce morbidity and over-treatment of low-risk patients, and providing intensive treatment for high-risk patients for whom survival remains poor. (Metzgar et al. 2005).

- The Importance of multidisciplinary management teams in pediatric solid tumors is clearly evident in the cooperative group’s trials that were constructed for Wilm’s tumor. Surgery plays a dual role in the management of pediatric solid tumors because it is required for establishing a histological diagnosis and for resecting the disease when possible and indicated. It is increasingly important that the surgeon work in a collaborative fashion with the pediatric oncologist and radiation oncologist because mutilating or disfiguring surgeries may no longer be indicated in the era of effective chemotherapy and radiotherapy. Significant advances in surgical and anesthetic management and postoperative supportive care have been complemented by substantial improvements in radiation planning and delivery.
AIM OF THE WORK

The aim of this work is to:

- Compare upfront nephrectomy (UN) for treatment of Wilms' tumor with radical nephrectomy after Preoperative Chemotherapy (PC) as regard the incidence and prevalence of perioperative complications.
- Provide the institutional experience of treatment of Wilms' tumor over 4 years duration in CCHE, that is based on the COG protocol, as regards the demographic, clinicopathological as well as surgical treatment variables.
- Assess the overall and disease free survival in both groups.
- Assess of safety and feasibility of UN in a unique set up, that is a highly specialized center in a developing country.
REVIEW OF LITERATURE
**EPIDEMIOLOGY**

In the United States, the annual incidence of renal tumors is about 8 cases per million children younger than 15 years, accounting for 7 percent of all childhood malignancies and for 500 new cases per year in North America. Wilms’ tumor is the most common renal malignancy in children under the age of 15 years, accounting for about 95 percent of all cases. Two-thirds of cases of Wilms' tumor are diagnosed before five years of age, and 95 percent before 10 years of age (Grovas A et al. 1997) (Perlman EJ 2005) (Linet MS et al. 1999)

In patients with unilateral involvement, the median age at diagnosis is 43 months in girls and 37 months in boys. Children with bilateral disease are diagnosed at an earlier age (median age, girls at 31 months and boys at 24 months). Patients with associated congenital anomalies, such as aniridia or genitourinary abnormalities, are also diagnosed at an earlier age. (Breslow NE et al. 1988). According to the Knudson two-hit model of tumorigenesis, the earlier age at onset of bilateral Wilms’ tumor represents a genetic predisposition to the disease. Wilms’ tumor in the adult population is rare, although numerous cases have been reported. (Knudson AG, Strong LC, 1972)

Girls have a slightly increased risk for Wilms’ tumor, with a male-to-female ratio of 0.92 to 1.00. The risk of developing Wilms' tumor varies among ethnic groups, with a greater risk in African-Americans and a lower risk in the Asian population. Epigenetic differences may contribute to the lower rate of disease in Asian children, as demonstrated by a study that reported infrequent loss of IGF2 imprinting in tumors from Asian patients. (Breslow NE et al. 1996)

Familial Wilms’ tumor is uncommon, occurring in only 1.5% of affected patients. Most cases of familial Wilms’ tumor occur in distant relatives,
rather than in parents or siblings. Sixteen percent of cases of familial Wilms’ tumor are bilateral, compared with 7% of sporadic cases. Unlike retinoblastoma, familial Wilms’ tumor is bilateral in only a small number of cases. Conversely, only a small proportion (3%) of cases of bilateral Wilms’ tumor is familial. The mean ages at diagnosis of familial unilateral and bilateral disease are 35 months and 16 months, respectively. (Kalapurakal JA et al. 2003) (Reinhard H et al. 2004)
GENETIC BACKGROUND

A prominent feature of WT is its association with specific congenital abnormalities and a variety of syndromes including: WAGR, Denys-Drash, and Beckwith-Wiedemann syndromes. (Grundy P et al. 1994)

**WAGR syndrome** — WAGR syndrome refers to the syndrome of Wilms' tumor, aniridia, genitourinary (GU) anomalies, and intellectual disability (mental retardation). Children with this syndrome have a constitutional chromosomal deletion of the WT1 gene located at 11p13. In a retrospective study of 54 children with WAGR syndrome, the following clinical findings were noted:

- Aniridia – 53 patients
- GU abnormalities (e.g., cryptorchidism, ambiguous genitalia) – 41 patients
- Intellectual disability – 39 patients
- Wilms' tumor – 31 patients
- Renal impairment (defined as glomerular filtration rate <80 mL/min) and proteinuria developed in 14 patients. (Fischbach BV et al. 2005)

**Denys-Drash syndrome** — The Denys-Drash or just Drash syndrome is a triad of progressive renal disease, male pseudohermaphroditism, and Wilms' tumor. Affected individuals have a germline point mutation in the eighth or ninth exon of the WT1 gene, which results in an amino acid substitution, and almost all patients (90%) will develop Wilms' tumor. The underlying renal pathology is diffuse mesangial sclerosis, which presents in infancy with proteinuria and progresses to nephrotic syndrome and renal failure. (Dharnidharka VR et al. 2001)
Beckwith-Wiedemann syndrome — Patients with the Beckwith-Wiedemann syndrome have a 5 to 10 percent chance of developing Wilms' tumors. This disorder is caused by microduplication mutations in the 11p15.5 region, site of a cluster of imprinting genes. The major clinical features of Beckwith-Wiedemann syndrome include macrosomia, macroglossia, omphalocele, prominent eyes, ear creases, large kidneys, pancreatic hyperplasia, and hemihypertrophy. (Koufos A et al. 1989)

Other congenital anomalies — Patients with other congenital syndromes and isolated congenital anomalies are also at risk for developing Wilms' tumors. These include:

- Perlman syndrome – Autosomal recessive overgrowth syndrome that is characterized by fetal gigantism, visceromegaly, unusual face, bilateral renal hamartomas with nephroblastomatosis, and Wilms' tumor. (Li M et al. 2001)
- Sotos syndrome – There is a 2 to 3 percent risk of Wilms' tumor in children with Sotos syndrome (also referred to as cerebral gigantism). Sotos syndrome is an overgrowth syndrome associated with facial, extremity, and cognitive abnormalities (Li M et al. 2001)
- Simpson-Golabi-Behmel syndrome – Simpson-Golabi-Behmel syndrome is an X-linked genetic disorder characterized with pre- and postnatal overgrowth with organomegaly, a distinctive course facial appearance described as a bulldog appearance, congenital heart disease, polydactyly, and a 7.5 percent change of developing Wilms' tumor. (Byrne J, Nicholson HS. 2002)
- Isolated hemihypertrophy.
- Isolated genitourinary abnormalities – Boys with Wilms' tumor may have cryptorchidism or hypospadias, while 10 percent of girls with Wilms' tumor have congenital uterine anomalies. Other kidney
abnormalities, such as renal ectopia or duplicated collecting systems, can also be seen.

- Familial Wilms’ tumor is rare and is associated with mutations in BRCA2 or TP53 (Li-Fraumeni syndrome).

Wilms’ tumor has been associated with loss of function mutations of a number of tumor suppressor genes. These include mutations of the WT1, p53, FWT1, and FWT2 genes, and at the 11p15.5 locus. The role of these gene mutations in the pathogenesis of Wilms’ tumor remains unknown. (Gao X et al. 2005)

- WT1 gene – The WT1 gene is located on chromosome 11p13. The WT1 gene product is expressed in the developing kidney, testis, and ovary. It appears to play a role in the development and differentiation of genitourinary tissues. High levels of WT1 result in suppression of growth-related genes, suggesting that WT1 may function as a tumor suppressor gene. The WT1 gene was the first identified genetic abnormality in children with Wilms’ tumor and was discovered in karyotypic analysis of children with WAGR syndrome. The 11p13 deletion in WAGR syndrome encompasses several contiguous genes, including the WT1 and PAX 6 (associated with aniridia) genes. In contrast, patients with Denys-Drash syndrome have a point mutation in the eighth or ninth exon of the WT1 gene resulting in their clinical findings. Less than 10 percent of patients with sporadic Wilms’ tumor have a WT1 gene mutation, suggesting that other mechanisms are involved. (Scholz H, Kirschner KM. 2005)

- 11p15.5 – The 11p15.5 locus (also referred to as the WT2 gene locus) contains a cluster of imprinted genes. Mutations at this locus have been identified in a number of syndromes characterized by either growth retardation or overgrowth including Beckwith-Wiedemann
syndrome (BWS). Imprinted genes are those that demonstrate selective gene expression based upon parental origin, such that either the paternal or maternal-inherited gene copy is expressed, but not both. As an example, in patients with BWS, the maternal copy of the Beckwith-Wiedemann (BW) gene is silenced during gametogenesis and only the paternal copy is expressed. As a result, offspring with BWS receive a mutation passed from their father and those who inherit a BW gene mutation from their mother are asymptomatic carriers, who can pass the mutation to their offspring. Patients with BWS and 11p15 gene mutations are at increased risk for Wilms' tumor. (Vuononvirta R et al. 2008)

- Somatic 11p15 defects have been found in Wilms' tumor cells, perilobar nephrogenic rests associated with Wilms' tumors, and some normal renal cells surrounding Wilms' tumors suggesting 11p15 mutations may play an early role in non-syndromic Wilms' tumorigenesis. In addition, one study demonstrated germ-line (constitutional) mutations in genes from this locus in the lymphocytes of 3 percent of non-syndromic Wilms' tumor patients (13 of 437 patients) and in one family with Wilms' tumors. No 11p15 defect was detected in the 220 controls. Patients with constitutional 11p15 defects compared to those without 11p15 mutations were more likely to have bilateral tumor involvement.

- p53 gene – The p53 tumor suppressor gene is located on chromosome 17p13.1. It encodes a nuclear protein, which acts as a transcription factor and blocks the progression of the cell cycle late in the G1 phase. P53 is the most commonly mutated gene in human cancer and is associated with a variety of malignancies including colorectal cancer, non-small cell lung cancer, osteosarcoma, and Ewing sarcoma. The p53 gene mutation is seen infrequently in
patients with Wilms' tumor and is associated with both favorable histological features and with unfavorable anaplastic histology. As a result, p53 mutations, which are used for prognosis in other malignancies, are not used as a biologic marker for prognosis in patients with Wilms' tumor.

- Familial WT genes – Familial Wilms' tumor accounts for 1 to 2 percent of cases. The mode of inheritance appears to be autosomal dominant with variable penetrance. In these families, there is no association with the WT1 gene mutations. Linkages have been demonstrated to the FWT1 gene locus at 17q12-2, the FWT2 gene locus at 19q13.3-q13.4, and at the 11p15.5 locus. (Turnbull C et al. 2012)

It remains unknown whether the presence of any of the above genes associated with Wilms' tumor affects response to therapy or is predictive of outcome. Limited data suggest that patients with WT1 germline mutations have a poorer outcome. This was illustrated in one study from the International Society of Pediatric Oncology (SIOP) that demonstrated patients with WT1 germline mutations had an increased risk for bilateral involvement, second tumor events, and a poor response to initial chemotherapy. The poor response correlated with stromal predominant tumors with rhabdomyomatous changes. However, further studies are needed before treatment stratification should be consider based upon the presence or absence of a WT1 germline mutation. (Fernandez C et al. Renal tumors. 2011) (Geller JI. 2008)
PATHOLOGY and MOLECULAR ASPECTS

Nephroblastoma, also known as Wilms tumor, is a malignant embryonal neoplasm that is derived from nephrogenic blastemal cells, with variable recapitulation of renal embryogenesis. Nephroblastoma has long been regarded as an illustration of the multiple-hit theory of oncogenesis that links malformations, premalignant lesions, and neoplasia (Knudson AG Jr, Strong LC. 1972). Extrarenal tumors with morphologic features of nephroblastoma have been reported in the retroperitoneum, sacrococcygeal area, testis, uterus, inguinal canal, and mediastinum (Wakely PE Jr, et al 1989).

(Table 1) Classification of renal tumors in children.

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<tr>
<td></td>
<td>Favorable histology</td>
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<tr>
<td></td>
<td>Anaplastic</td>
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<tr>
<td></td>
<td>Cystic partially-differentiated nephroblastoma</td>
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<td>Nephrogenic rests and nephroblastomatosis</td>
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<td>Metanephric tumors</td>
<td>Metanephrinc adenoma</td>
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<td>Metanephrinc adenofibroma</td>
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<td>Metanephrinc stromal tumor</td>
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<td>Mesenchymal tumors</td>
<td>Clear cell sarcoma</td>
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<td>Rhabdoid tumor</td>
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<td>Congenital mesoblastic nephroma</td>
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<td>Renal epithelial tumors</td>
<td>Papillary renal cell carcinoma</td>
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<td>Renal medullary carcinoma</td>
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<td>Renal tumors associated with Xp11.2 translocations</td>
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( Adopted from Khoury, J. D. 2005)

Macrosopic features

Grossly, most Wilms' tumors are large nodular solitary lesions. However, 5 to 7 percent of patients have bilateral renal involvement and 10 percent have multifocal loci within a single kidney. Wilms' tumor usually compresses the adjacent normal renal parenchyma, forming a pseudocapsule composed of compressed, atrophic renal tissues. This finding may be a helpful aid in distinguishing nephroblastoma from hyperplastic nephrogenic rests, which
lack a surrounding pseudocapsule. Gross characteristics of nephroblastoma vary and reflect the differential predominance of stromal and nonstromal components in individual tumors. Whereas nephroblastomas commonly is pale gray or tan and has a soft consistency, tumors that consist predominantly of stroma may be white and firm. Cyst formation varies and may be prominent in certain cases. (Yanai T et al. 2004).

The texture of the tumors varies, depending on the predominant histological pattern. Many are soft and friable with necrotic or hemorrhagic areas frequently noted. This consistency increases the risk of intraoperative tumor rupture. (Breslow et al, 1988).

Rare cases of so-called “botryoid nephroblastoma” that are localized almost exclusively to the renal collecting system have been described (Yanai T et al. 2004).

![Figure 1 Gross appearance of classic WT (Nephroblastoma); nodular and well-circumscribed, obliterating most of the native kidney. (Courtesy of B.B. Dahms, MD, Cleveland, OH.)](image)

**Microscopic features**

The origin of the tumor is the metanephrogenic blastema; thus the histology mimics the development of a normal kidney, showing the three tissue components: blastema, epithelium, and stroma—that are present in most tumors, in varying proportions. One hallmark of nephroblastoma is its
marked histologic diversity, which may be seen in any of the components and may lead to diagnostic difficulties in certain cases.

**Blastemal cells** are small, round, densely packed, with scant cytoplasm and minimal evidence of differentiation. Mitotic figures usually are numerous. The blastemal component often exhibits various growth patterns, including serpentine, nodular, diffuse, and basaloid.

An **epithelial component** in the form of primitive tubular and occasional glomeruloid structures that recapitulate the developmental stages of metanephric tubules, are encountered most commonly. Differentiated epithelial structures are not uncommon, especially in posttherapy specimens. Nephroblastomas with squamous, mucinous, or ciliated epithelial components are observed occasionally.

Nephroblastomas exhibit significant diversity in the relative abundance and patterns of differentiation of the **stromal component**. Most commonly, the stroma is composed of spindle cells with a myxoid background that resembles embryonal mesenchyme. Skeletal muscle tissue at various stages of maturation constitutes the most common line of heterologous stromal differentiation and occasionally may be extensive. Nevertheless, the scope of stromal differentiation in nephroblastoma is wide and includes smooth muscle, cartilage, bone, adipose tissue, and neural tissue. *(Khoury, J. D. 2005)*

Because Wilms’ tumor can be recognized with standard hematoxylin and eosin staining, the role of ultrastructural or immunohistochemical studies is limited.
Microscopic features as a prognostic factor

Overall, approximately 5% of nephroblastomas have unfavorable histology; this denotes tumors with anaplastic cells that are characterized by the following: significant nuclear enlargement, nuclear hyperchromasia, and enlarged multipolar mitotic figures. Anaplasia may occur in the blastemal, epithelial, or stromal components. (D’Angio GJ et al. 1989)(Beckwith JB, Palmer NF. 1978).

On a genomic level, nuclear enlargement and hyperchromasia are manifestations of increased cellular DNA content, whereas atypical mitotic figures seem to reflect disruption of cellular genomic integrity with resultant mitotic errors and elevated mutability rates. Although p53 mutations are not common in nephroblastoma, when present, they are associated strongly with foci of anaplastic morphology. Furthermore, detection of p53 overexpression by immunohistochemistry was associated with anaplastic morphology and worse outcome. (Cheah PL et al. 1996)

Unfavorable histology is more common in Blacks than in other races, and it is rare in patients who are younger than 2 years of age; it increases gradually to a plateau of approximately 13% in patients who are 5 years of age and older. (Zuppan CW et al. 1988)

Histologic characterization of nephroblastoma evolved from the recognition of an association between anaplastic features and poor clinical outcome. Whereas standard
treatment regimens for nephroblastomas result in high cure rates in most cases, patients who have tumors that exhibit unfavorable histology have a significantly lower failure-free survival rate, despite intensive chemotherapy and radiation therapy. Notably, the prevalence of unfavorable histology in nephroblastoma varies by race and age.

Anaplasia is considered to be a harbinger of resistance to chemotherapy, and its prognostic significance seems to be more profound when it is distributed diffusely and identified at advanced disease stages. Accordingly, the distinction between focal anaplasia and diffuse anaplasia has permitted better stratification of patients for therapeutic and prognostic purposes. **Focal** anaplasia refers to the presence of one or a few localized foci of anaplasia within a primary tumor, without evidence of concomitant widespread nuclear atypia.

In contrast, criteria for **diffuse** anaplasia are met when one or more of the following is present: (1) nonlocalized anaplasia or anaplasia beyond the tumor capsule; (2) anaplastic cells present in intrarenal or extrarenal vessels, renal sinus, extracapsular invasive sites, or metastatic sites; (3) focal anaplasia with nuclear unrest present elsewhere in the tumor. (Vujanic GM et al. 1999).

Occasionally, nephroblastoma with **favorable histology** may exhibit nuclear enlargement and hyperchromasia in the absence of detectable enlarged multipolar mitotic figures.

**A recent Japanese study** had shown that the blastema-predominant subtype of WT (BPT-WT) is a strong predictor of poor prognosis and such patients must be treated as high risk group irrespective of the stage. (Aoba T et al. 2012)

Such morphologic findings have been called “**nuclear unrest**.” Although tumors with nuclear unrest may represent an intermediate stage in a continuum from favorable to unfavorable histology, they seem to be more akin to tumors with favorable histology from clinical and biologic
standpoints; however, widespread nuclear unrest that is associated with focal anaplasia does constitute diffuse anaplasia. (Khoury, J. D. 2005)

The distribution of histological subtypes is different following preoperative chemotherapy compared with primary surgery, with differentiation of the tumor occurring after chemotherapy. Stromal and epithelial predominant tumors are found more often after treatment with preoperative chemotherapy. These histological subtypes may demonstrate a poor clinical response to therapy but have an excellent prognosis if the tumor is completely excised. Patients with progressive disease have a poor prognosis, and these patients will require treatment with a different chemotherapeutic regimen (Ritchey et al, 1994; Ora et al, 2007).

Metastatic nephroblastomas
Metastatic nephroblastoma may be composed of a single component or a combination of components that are present in the primary tumor. Not uncommonly, lymph nodes with or without apparent metastatic tumor may contain amorphous proteinaceous material within the nodal sinusoidal system. The same material usually is identified within glomeruli and tubules in the corresponding nonneoplastic renal parenchyma. Such material alone, in the absence of unequivocal metastatic nephroblastomas cells, is not evidence of metastatic disease. Morphologic effects of therapy Posttherapy changes in nephroblastoma generally include a dramatic reduction in actively proliferating embryonal cells (blastema and primitive epithelium) and disproportionate persistence of mature tubular and skeletal muscle cells. (Boccon-Gibod L et al. 2000) Generally, anaplastic tumor cells are unaffected by therapy and their presence should be documented in any posttherapy specimen with residual tumor. Immunophenotypic features Immunohistochemistry is of limited usefulness in the diagnosis of nephroblastoma. Nuclear immunostaining with WT1 generally is identified

Patterns of Spread
Wilms' tumor can spread both locally and hematogenously. Local spread typically occurs into the renal hilar structures and may penetrate the renal capsule. These tumors also have a propensity to invade the renal vein and form thrombi in the inferior vena cava, sometimes progressing as far as the right atrium. Local and distant lymph node involvement can occur. The most common sites of hematogenous metastasis are the lungs and liver.

Nephrogenic Rests
A peculiar feature of Wilms' tumor is its association with nephrogenic rests, foci of primitive but nonmalignant cells whose persistence suggests a defect in kidney development. These precursor lesions are found within the normal kidney tissue of 30% to 40% of children with Wilms' tumor.

Nephrogenic rests (NRs) have a varied natural history, and most do not form Wilms tumor. A rest can undergo maturation, sclerosis, involution, or complete disappearance. Nephrogenic rests have also been detected in 1% of kidneys in infants on postmortem exam, a much higher incidence than that of Wilms' tumor. Hence, most (NRs) apparently undergo involution (Beckwith, 1998).

NRs can be separated into two fundamentally distinct anatomical categories: perilobar nephrogenic rests (PLNRs) and intralobar nephrogenic rests (ILNRs) (Beckwith et al, 1990) according to their location within the renal lobe. Relative position within the lobe is a direct reflection of the
chronology of the embryologic development of the kidney. PLNRs are found only in the lobar periphery, which is elaborated late in embryogenesis, while ILNRs are found anywhere within the lobe, as well as the renal sinus and the wall of the pelvicalyceal system. Therefore ILNRs are generally believed to be the result of earlier gestational aberrations (Beckwith et al, 1998).

Of particular interest is the observation that PLNRs are usually found in children with BWS, while ILNRs are typically seen in children with aniridia, WAGR, and DDS or other features associated with WT1. The age at diagnosis is lower for Wilms' tumor associated with WT1 mutations, and those arising in association with ILNR. Multiple rests in one kidney usually implies that NRs are present in the other kidney (Beckwith, 1990). Children less than 12 months of age who are diagnosed with Wilms' tumor and also have NRs, in particular PLNRs, have a markedly increased risk of developing contralateral disease and require frequent and regular surveillance for several years (Coppes et al, 1999). Surveillance is also recommended for those diagnosed after 12 months of age who have NRs (D'Angio et al, 1993). The occurrence of metachronous Wilms' tumor in patients previously treated with conventional chemotherapeutic regimens suggests that nephrogenic rests are not always eradicated.

The appearance of the NRs can provide some help in distinguishing between them and Wilms' tumor. The Wilms' tumor will have a spherical shape, while hyperplasic rests will retain the appearance of the original rest and be more elliptical or lenticular in shape. MRI may be of some value in distinguishing between the two lesions, but this needs to be confirmed prospectively in large numbers of patients (Rohrschneider et al, 1998; Hoffer, 2005). Nephroblastomatosis refers to the presence of multiple nephrogenic rests. Diffuse overgrowth of PLNRs may produce a thick rind that enlarges the kidney but preserves its original shape.
There are four types of nephrogenic rests (NRs) including dormant, sclerosing, hyperplastic, or neoplastic. While dormant and sclerosing rests are usually microscopic and do not have malignant potential, hyperplastic and neoplastic rests are grossly visible and do have malignant potential (Murphy et al. 1994).
STAGING SYSTEMS

Staging criteria for Wilms' tumor are based upon the anatomic extent of the tumor without consideration for genetic, histological, or biological markers. Higher stages represent more extensive disease with a worse prognosis. As a result, more aggressive therapeutic regimens are generally administered to patients with higher tumor stages. (D'Angio GJ 2003)

There are two major systems currently in use:

- National Wilms' tumor Study (NWTS) – The NWTS system is based upon surgical evaluation prior to the administration of chemotherapy. It is used throughout the United States and Canada.
- International Society of Pediatric Oncology (SIOP) – The SIOP system is based upon post-chemotherapy surgical evaluation and is used extensively in Europe.

(See Table 2) Stage for stage comparison of staging systems for WT

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<tr>
<th>Stage</th>
<th>NWTS (before chemotherapy)</th>
<th>SIOP (after chemotherapy)</th>
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| I     | (a) Tumor is limited to the kidney and completely excised  
(b) The tumor was not ruptured before or during removal  
(c) The vessels of the renal sinus are not involved beyond 2 mm  
(d) There is no residual tumor apparent beyond the margins of excision | (a) Tumor is limited to kidney or surrounded with fibrous pseudocapsule if outside of the normal contours of the kidney, the renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface, and is completely resected (resection margins “clear”)  
(b) The tumor may be protruding into the pelvic system and “dipping” into the ureter (but it is not infiltrating their walls)  
(c) The vessels of the renal sinus are not involved  
(d) Intrarenal vessel involvement may be present |
| II    | (a) Tumor extends beyond the kidney but is completely excised  
(b) No residual tumor is apparent at or beyond the margins of excision  
(c) Tumor thrombus in vessels outside the kidney is stage II if the thrombus is removed en bloc with the tumor | (a) The tumor extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins “clear”)  
(b) The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but is completely resected  
(c) The tumor infiltrates adjacent organs or vena cava but is completely resected |
| III | Residual tumor confined to the abdomen:  
(a) Lymph nodes in the renal hilum, the periaortic chains, or beyond are found to contain tumor  
(b) Diffuse peritoneal contamination by the tumor  
(c) Implants are found on the peritoneal surfaces  
(d) Tumor extends beyond the surgical margins either microscopically or grossly  
(e) Tumor is not completely resectable because of local infiltration into vital structures  
(f) Tumor biopsy | (a) Incomplete excision of the tumor, which extends beyond resection margins (gross or microscopical tumor remains postoperatively)  
(b) Any abdominal lymph nodes are involved  
(c) Tumor rupture before or intraoperatively (irrespective of other criteria for staging)  
(d) The tumor has penetrated through the peritoneal surface  
(e) Tumor thrombi present at resection margins of vessels or ureter, transected or removed piecemeal by surgeon  
(f) The tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery |
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<td>IV</td>
<td>Presence of hematogenous metastases or metastases to distant lymph nodes</td>
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<td>V</td>
<td>Bilateral renal involvement at the time of initial diagnosis</td>
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Both systems accurately predict clinical outcome and reflect therapeutic differences between the two cooperative groups. The COG approach allows adequate assessment of the extent of disease and histological characteristics of the tumor and facilitates the collection of tumor tissue for biologic studies prior to therapy. The SIOP approach uses preoperative chemotherapy, decreasing the volume of tumor and thereby decreasing the perioperative risk of tumor spillage.

Fernandez et al. had reported a retrospective analysis of the use of FNAC prior to initiating neoadjuvant chemotherapy, as a possible adjunct to imaging to lessen the incidence of misdiagnosis, that’s evident in the SIOP pathway. They correlated the results of FNAC of 66 patients of unilateral Wilms’ tumor with the resected specimens. Fifty eight patients had positive FNAC, 57 of them were found to have correct diagnosis of WT (PPV: 98.2%). Within the group of negative FNAC (n=8), 3 cases were false negative i.e Wilms’ tumor (NPV: 62.5%). Sensitivity was 95% and specificity was 83.3%. They concluded that FNAC is a useful and feasible technique in children that may confirm the suspected diagnosis of unilateral WT, avoiding inadequate preoperative chemotherapy in case of a non-Wilms renal tumor. *(Fernandez I et al. 2011)*
The surgeon is responsible for determining tumor extent. Accurate staging is essential for the subsequent determination of the need for radiation therapy and the appropriate chemotherapy regimen.

The ability of CT to stage tumors accurately has been questioned by some radiologists (Damgaard-Pedersen K et al 1998) especially by correlation with post operative histopathologic findings (Gow KW et al 2000). In the latter study, they found that CT has difficulty discriminating between Stage I and Stage II disease. Since, both stages would receive similar therapy, the result of overstaging this group would not have been clinically significant. However, the distinction between Stage II and III is more crucial because the latter might be considered for primary chemotherapy if primary surgery is felt to be too hazardous. The consequences of over- or understaging are obvious, especially considering the potential side effects of radiotherapy such as intestinal stricture, ulceration, perforation, hematochezia, bone growth arrest, or osteonecrosis. (Gow KW et al 2000)

There was a consistent difficulty in determining capsular involvement or nodal involvement by CT examination. Effacement of the perirenal fat planes is not sufficient to diagnose penetration, and tumor size is unhelpful. Irregular soft tissue outside the capsule is the most common finding with disruption, but the observation can be subtle. With respect to nodal involvement, associated lymph node enlargement may be reactive, whereas nodal involvement may be occult at both CT and surgery. In the aforementioned study, CT staging agreed with histological staging in less than half the cases. They therefore continue to advocate initial nephrectomy for histological staging of unilateral nonmetastatic disease. (Gow KW et al 2000)
SURGICAL ANATOMY

Wilms' tumor surgery requires meticulous planning and sophisticated surgical technique. Detailed anatomical knowledge can facilitate the performance of nephrectomy and cannot be replaced by advanced and sophisticated imaging techniques. Removal of a large nephroblastoma can still be a demanding task. Large trials in WT surgery have identified various anatomy-based complications. Two main goals can be defined from surgical treatment: exact staging as well as safe and complete resection of tumor without spillage.

Surgical anatomy of the urogenital system entails the following subtitles:

- Embryogenesis (normal development – congenital anomalies)
- General topographic features
- Relations

**Embryogenesis of the Kidneys and Ureters**

**Normal Development**

Three excretory organs (pronephroi, mesonephroi, and metanephroi) develop from the intermediate mesoderm. The pronephroi are never functional in human embryos and degenerate on days 24 or 25. The mesonephroi ("interim or temporary kidneys") appear late in the 4th week (day 24 or 25) just caudal to the pronephroi. The mesonephroi have a brief functional period from the late embryonic to the early fetal period (weeks 6 to 10), during which they produce very dilute urine. The mesonephroi take over a portion of the pronephric duct in the thoracic and upper lumbar regions, making it the mesonephric (or Wolffian) duct. The mesonephric tubules form excretory units: the medial end forms Bowman's capsule; lateral branches from the aorta form capillaries that become glomeruli which
fit into Bowman's capsule, thus forming renal corpuscles. The tubules open into mesonephric ducts. The **metanephroi** ("hind kidneys") are the final developmental stage. The metanephric diverticulum (ureteric bud) arises on day 35 from the caudal part of the mesonephric duct. This entity is destined to give rise to the collecting apparatus of the urinary system which consists of 1-3 million collecting tubules, minor and major calices, the renal pelvis, and ureters. The metanephrogenic blastema (metanephric mesoderm) forms from the caudal portion of the intermediate mesoderm and gives rise to the nephrons (800,000 to 1,000,000 in each kidney). Blastema tissue capping each arched collecting tubule differentiates into the nephron. Glomeruli form and are enveloped by Bowman's capsule to form the renal corpuscle. The proximal convoluted tubule, loop of Henle, and distal convoluted tubule form the remainder of the nephron. The distal convoluted tubule opens into the arched collecting duct.

When the kidneys ascend from the pelvis to their permanent location in the upper lumbar region, they come into apposition with the adrenal glands, which develop in situ. During ascent, the kidneys rotate medially so that the hilum, which initially faced anteriorly, now faces medially. (J Skandalakis, G Colborn' Skandalakis' Surgical Anatomy. Mcgraw- Hill. 2006.)

**Wilms' tumor** originates from the metanephros (mesodermal precursors of renal parenchyma) or occasionally from mesonephric remnants within the extrarenal retroperitoneum (Shamberger 1999).
**Congenital Anomalies**

**Renal agenesis** is caused by failure of the ureteric bud to develop or by early degeneration of the bud. More on the left side. May be unilateral or bilateral. The bilateral variety is incompatible with life. *(Hill LM et al 2000)*

**Non-rotation or abnormal rotation:** Non-rotation results in the hilum facing anteriorly. With excessive rotation, the hilum faces posteriorly; it may face laterally if rotation occurs in the wrong direction. Abnormalities of rotation are often associated with ectopic kidneys.

**Ectopic kidneys** may be unilateral or bilateral. Most are located inferior to their normal location, with the hilum facing anteriorly. Most ectopic kidneys lie in the pelvis; some are found in the lower abdomen. Pelvic kidneys often fuse to form pancake (discoid) kidneys. In crossed renal ectopia, one kidney has crossed to the contralateral side. The blood supply of ectopic kidneys is often from multiple arteries which arise from nearby arteries such as the internal iliac, the external iliac, and/or the aorta. *(Kubricht WS et al 1999)*

**Horseshoe kidney** occurs in 1 in 500 births. There is a seven percent incidence of horseshoe kidney in individuals with Turner's syndrome; children with this condition are 2 to 8 times more likely to have Wilms' tumors. In horseshoe kidney, the caudal poles fuse across the midline. Usually the horseshoe lies in the hypogastrium anterior to the lower lumbar vertebrae because of the failure of ascent which occurs when the kidney is 'hung up' on the inferior mesenteric artery. Horseshoe kidney is usually symptomless. **Various duplications of the urinary tract** may occur. **Supernumerary kidney** is rare; it is probably due to two ureteric primordia forming on one side. *(Peng HC, Chen HC 2000)*
The kidneys are paired, bean-shaped organs located on either side of the vertebral column in the perirenal compartment of the retroperitoneal space between the anterior and posterior leaflets of the renal fascia (Gerota's fascia). A stroma of adipose tissue (thick or thin) covers all their surfaces.

The adult kidney has a length of 10-14 cm, width of 5-7 cm, and thickness of 2.5-3.0 cm. Its approximate weight is 135 g in women and 150 g in men.

Each kidney has two surfaces (anterior and posterior), two borders (lateral and medial), and two poles (superior and inferior); each kidney also has its own relations with several other anatomic entities. The kidney is related anteriorly to the abdominal viscera and posteriorly to the osteomuscular area. The right kidney lies at a lower level in comparison with the left, a phenomenon that permits the right lower pole to be palpable.

When the patient is in the recumbent position, the kidneys may extend from T12 to L3, but in the erect position both may extend from L1 to L4. In addition to changing with alterations in posture, the kidneys may move upward and downward approximately 1-7 cm with respiration. The above numbers represent, if the term is permissible, the "physiologic" movements of the kidney, not the ptotic (nephroptotic, mobile, floating) kidney. (O'Rahilly R., Gardner G 1986.)

The anterior surfaces of both kidneys are covered by the following anatomic entities: Perirenal fat - Gerota's fascia - Pararenal fat - Parietal posterior peritoneum (partially). The anterior surface of the right kidney is related to: Right adrenal gland – Liver - Second part of duodenum - Inferior vena cava – Ureter - Ascending colon - Hepatic flexure of the colon. The
anterior surface of the left kidney is related to: Left adrenal gland – Pancreas - Splenic vessels – Stomach – Spleen - Duodenojejunal flexure - Ligament of Treitz - Inferior mesenteric vein - Descending colon - Splenic flexure of the colon - Loops of jejunum.

**Posterior surfaces Right kidney:** the 12th rib, with the superior pole extending upward into the 11th intercostal space. **Left kidney:** the 11th and 12th ribs.

**Lateral Border** Related to the perirenal fat, Gerota's fascia, and pararenal fat. From a surgical standpoint, the lateral renal border is not important.

**Medial Border** In the medial border of each kidney there is a vertical fissure called the renal porta or hilum. The renal arteries and nerves enter through the renal hilum, while the veins, lymphatics, and proximal ureter exit through it. For all practical purposes the concavity of the hilum is continuous with a deep declivity in the medial border of the kidney, the so-called renal sinus. This recess is lined by the tissues of the renal capsule and envelops the renal vessels and the renal pelvis. (*Fine H et al 1966*)

As one proceeds centrally from the peripherally located reddish brown parenchyma of the kidney, the renal sinus is encountered. Here the vascular structures and collecting system coalesce before exiting the kidney medially. These structures are surrounded by yellow sinus fat, which provides an easily recognized landmark during renal procedures such as partial nephrectomy. At its medial border, the renal sinus narrows to form the renal hilum. It is through the hilum that the renal artery, renal vein, and renal pelvis exit the kidney and proceed to their respective destinations.

Within the renal sinus is the renal pelvis, a funnel-shaped sac formed by the widely expanded portion of the proximal ureter and by the junctions of the
major calices. The term 'intrarenal pelvis' denotes a pelvis that is almost covered or completely covered by renal parenchyma. This term is in general use among reconstructive renal surgeons. The renal pelvis bifurcates or trifurcates within the sinus producing two or three major calices. Each of the major calices again subdivides into 7 to 14 minor calices which receive the collecting tubules (approximately 500). The renal pelvis most commonly lies posterior to the renal vessels. Occasionally it may be situated between or in front of the vessels. In some instances the renal pelvis is small, lacks an extrarenal portion, and is located entirely within the renal parenchyma.

The **upper pole** of each kidney is related to its associated adrenal gland, separated from it only by a thin diaphragm of connective tissue originating from the fascia of Gerota, which totally envelopes each adrenal. The right and left adrenal glands are located superomedially at the front of the upper part of each kidney.

In a report by Davie, 6 out of 1500 necropsies had their fixed with the upper pole of the kidney in such a way that a nephrectomy would necessarily include the adrenal glands. This knowledge is critical for a surgeon undertaking laparoscopic adrenalectomy. The laparoscopic operation can be undertaken safely, though, according to the report of Prinz comparing laparoscopic adrenalectomy with open adrenalectomy. The lower pole is occasionally located close to the lumbar triangle. *(Prinz RA. 1995)*
Arterial Supply

The paired (right and left) renal arteries originate from the lateral wall of the aorta just below the origin of the superior mesenteric artery at the level of the intervertebral disc between the L1 and L2 vertebrae. However, the origin of the longer right renal artery is more posterior in comparison to the left. Rarely, the right renal artery originates from the posterior wall and travels posterior to the inferior vena cava to reach the right kidney. The inferior suprarenal artery and the artery for the renal pelvis and proximal ureter arise from each renal artery prior to its terminal divisions.

When dissected 30 adult abdominal aorta specimens from cadavers, Ozan et al. reported the origin of the renal arteries from the aorta. The ostium of the right renal artery was more cranial than the ostium of the left renal artery (53.3%). However, the ostia of both right and left renal arteries were at the same level in three cases (10%). Locations of the ostia of the renal arteries were usually on the lateral and anterolateral regions of the aortic wall. (Glikman L et al 1989).

Each artery reaching the hilum divides into anterior and posterior divisions in relation to the renal pelvis, finally giving rise to the following terminal branches supplying the four renal segments: (1) apical (superior), (2) anterior (subdivided into superior and inferior), (3) posterior, and (4) basilar (inferior). These are the renal segmental arteries. Each segmental artery supplies a distinct portion of the kidney with no collateral circulation between them. Thus occlusion or injury to a segmental branch will cause segmental renal infarction. Different authors give different names to the
segments. Also, different authors refer to the segmental arteries by different names, such as "suprahilar" instead of "apical." Graves stated that aberrant renal arteries are normal segmental arteries and not accessory arteries.

**Surgical tips:**

- The very short apical artery supplies the anterior and posterior surfaces of the apical segment.
- The basilar artery provides blood for the anterior and posterior surfaces of the basilar segment.
- The anterior segment is supplied by two branches: one for its superior part and another for its inferior part.
- The blood supply of the posterior segment is provided by a single artery.

The "avascular" line or plane (also known as Brödel's line) is the most avascular area of the kidney. It is located slightly behind the convex border at the posterior half of the kidney at the junction of the area supplied by the anterior and posterior divisions of the renal artery. This is approximately 2/3 of the way along a line from the hilum to the lateral margin of the kidney. Incision in this area will permit removal of a stone within the renal calices with minimal damage.

According to Banowsky, **unilateral multiple renal arteries** occur in approximately 23 percent of the population. Another 10 percent have bilateral multiple arteries. Multiple renal arteries are more common on the left side. Banowsky differentiates between **multiple** and **accessory** renal arteries. He states that multiple renal arteries supply one renal segment and accessory arteries supply only part of the segment. He emphasizes that it is advisable to ligate only the accessory arteries. *(Novick, Andrew C. et al. 1989)*.
Singh et al stated that accessory renal arteries are more common on the left side, occurring in as many as 30-35% of cases and usually entering the upper or lower pole of the kidney. Such an accessory artery of the lower pole may produce ureteric obstruction with secondary hydronephrosis. (Singh G et al 1989) Ligation of an accessory renal artery can result in the production of an area of infarction of variable size, though often small. Renovascular hypertension may occur as a sequelae of the ischemia.

**Venous Drainage**

The kidney is drained by several veins which together form the renal vein. The left renal vein is longer than the right. It receives blood from the left adrenal, the left gonad, and the body wall, including the diaphragm. The left adrenal vein enters the renal vein superiorly; the left gonadal vein enters inferiorly. Usually one or two lumbar veins empty into the posterior wall of the left renal vein.

The renal vein is located directly anterior to the renal artery, although this position can vary up to 1 to 2 cm cranially or caudally relative to the artery. The right renal vein is generally 2 to 4 cm in length and enters the right lateral to posterolateral edge of the IVC.

Unlike the arterial supply, the venous drainage communicates freely through venous collars around the infundibula, providing extensive collateral circulation in the venous drainage of the kidney. Surgically, this is important because unlike the arterial supply, occlusion of a segmental venous branch has little effect on venous outflow.

Temporary or permanent occlusion of the left renal vein close to its entrance into the inferior vena cava can usually be done with impunity.
Aluisio et al. studied the normal and anomalous anatomy of the left renal vein and its tributaries in 20 cadavers. They reported the following:

- Other than the left suprarenal (adrenal) and left gonadal veins, the left renal vein had no additional tributaries
- Study of the left suprarenal and left gonadal veins revealed no direct connections to the inferior vena cava

Anomalies of the left renal venous drainage system:

- Anomaly of the left renal vein itself manifested as a supernumerary left renal vein
- Bifurcation of the gonadal vein
- Bifurcation of the suprarenal vein
- Inferior phrenic vein draining into the left renal vein distal to the superior mesenteric artery
- Lumbar vein drainage into the left renal vein that may represent either an anomaly or a normal variation
- Aluisio et al found no evidence of a systemic collateral flow system for drainage of the left kidney following left renal vein division. (Aluisio FV et al, 1991)
- Unlike the left renal vein, the short right renal vein contains a thin valve which is not good material for suture. Therefore, in addition to excising the right renal vein during right sided nephrectomy, the surgeon should excise a small cuff of the medial wall of the inferior vena cava where the right renal vein enters. Multiple renal veins are not common and left renal vein duplication is rare.
- The left and right kidneys show a difference in venous drainage. In right- sided nephroblastoma with cava thrombus, ligature and dissection of the left renal vein is possible. In the majority of patients,
sufficient venous collaterals via the phrenic, adrenal, hemiazygos, testicular, lumbar and ureteral veins are present. In contrast, the anatomy of the right kidney does not allow this maneuver. In humans, embryogenesis of the renal and post renal segments of IVC involves the sequential appearance of three paired venous channels: the posterior cardinals as well as the sub cardinal and supra cardinal veins. The development of anastomotic channels between these channels and subsequent regression of segments of this system might be impaired, leading to variants like the persistence of the left sub cardinal vein leading to a high confluence of the large veins. Other rare anomalies of the IVC include duplication, left-sidedness of the vein and interruption of the IVC. Ligature and cutting of the large renal vessels is one of the most important steps of nephrectomy. Early ligature of the vein has the theoretical advantage of preventing hematogenous tumor spread. However, this was never confirmed by a prospective trial. On the other hand, primary ligature of the artery is recommended for prevention of tumor swelling and rupture. There is no consensus in literature regarding the sequence of vessel ligature. Selected international standard publications recommend early control of the hilum. However, this is often not feasible with extremely large tumors; mobilization of the tumor mass must first occur to allow exposure of the hilar vessels. The current SIOP 2001/German Society of Pediatric oncology protocol recommends initial ligature of the artery. When feasible, we follow this recommendation. During removal of left renal tumors, damage to the aorta, superior mesenteric artery (SMA), and right renal artery has been reported to occur. These vessels are in close proximity to the tumor mass, and if the aorta and IVC separate by tumor or lymphatic infiltration, they are threatened during removal of the left kidney. The left renal vein is usually
identified first. Once it is divided another artery is revealed underneath that could be the superior mesenteric artery, aorta, or left or right renal artery. This artery should not be ligated until its exact identity has been established. When in doubt, this can be done by cross-clamping the vessel with a vascular clamp. It can be clearly stated that attempts at early ligation of the hilar vessels cannot be justified until the renal vasculature is clearly identified. The vessels most at risk during excision of right renal tumors are IVC and contralateral renal vein. In large right-sided tumors, the IVC enters the tumor mass and is hidden from vision. Under this circumstance, the right renal artery is in close proximity to the left renal vein, which can thus be damaged. If unrecognized, such damage can lead to venous infarction and loss of renal function. A coincident left IVC with right sided WT has been reported, a case in which the IVC drains into the left renal vein, then crossed the middle line, in front of the Aorta, to continue upwards, as right sided supra-renal IVC to the right atrium. (K Burney et. al 2005)
**Lymphatics**

The renal lymphatic network is very rich. The renal lymphatics follow the blood vessels and form large lymphatic trunks. The trunks exit through the renal sinus where they receive communicating lymphatics from the renal capsule and perinephric fat. Lymphatics from the renal pelvis and upper ureter communicate with others at the renal hilum. Two or three lymph nodes close to the renal vein accept the lymph and then drain to the paraaortic lymph nodes.

The lymphatics of the right kidney drain into lymph nodes located between the inferior vena cava and the aorta, lateral paracaval nodes, and anterior and posterior inferior vena caval lymph nodes. They also drain upward toward the right diaphragm, and downward to the common iliac lymph nodes. Other pathways are into the thoracic duct or crossing the midline into the left lateral aortic lymph nodes.

The lymphatics of the left kidney drain into the lateral paraaortic lymph nodes and anterior and posterior aortic lymph nodes. They also travel upward to the diaphragm and downward to lymph nodes associated with the inferior mesenteric artery. According to Kabalin, malignancy of the left kidney does not metastasize to the nodes between the inferior vena cava and aorta except in advanced disease. (Kabalin JN. Surgical anatomy of the retroperitoneum, kidneys, and ureters. 1998)
The retroperitoneum is bounded posteriorly by the abdominal wall, which consists of the lumbodorsal fascia and the enclosed sacrospinalis and quadratus lumborum muscles. Laterally, the retroperitoneum is contiguous with the preperitoneal fat and is bounded laterally by the transversus abdominis musculature of the lateral abdominal wall. The peritoneum is the anterior limit, whereas cranially the diaphragm limits the retroperitoneum. Caudally the retroperitoneum is contiguous with the extraperitoneal pelvic structures.

According Farthmann, the retro peritoneum can be divided into three zones and four parts: the central zone (containing the aorta, inferior vena cava, pancreas, and duodenum); two lateral zones (the kidneys, ureters, and ascending/descending colon), and the pelvic zone (rectosigmoid, iliac vessels, and urogenital organs). Three compartments of retro peritoneal space are related to the kidney: the perirenal space as well as the anterior and posterior pararenal spaces. The perirenal space is the home of the kidneys. The renal fascia, a collagenous connective tissue of mesodermal origin that envelopes the kidney, is responsible for this compartmentalization. The kidney is enveloped by the anterior and posterior laminae of the renal fascia and fatty tissue inside and outside the fascia. There is some medial fixation with the adventitial covering of renal vessels and aorta or inferior vena cava (IVC). (Farthmann, et al. 1989)
The rate of perirenal infiltration of nephroblastomas remains unclear. To obtain clear margins, a rim of healthy tissue including covering fibrous tissue and fat has to be resected with the tumor. Strict orientation between different retroperitoneal planes is required to achieve this. Standard textbooks recommend that the tumor plane should be developed outside the perirenal fascia. In other words, resection of the tumor-bearing kidney during radical uretero-nephrectomy also requires removal of the intact Gerota’s and Zuckerkandl’s fascia that cover the kidney. This procedure is known as a perifascial nephrectomy. At the upper pole of the kidney, a fascial septum separates the adrenal gland from the kidney. The adrenal gland for small or lower pole tumor can be spared. However, in many cases, when the tumor is large and adrenal gland is attached it must be removed to achieve adequate margins. (Ross JH et al 1999)

**Posterior Abdominal Wall**

**Posterior Musculature and Lumbodorsal Fascia**

The quadratus lumborum and sacrospinalis muscles form the muscular portion of the posterior abdominal wall, filling the space among the 12th rib, spine, and iliac crest.

The lumbodorsal fascia surrounds the sacrospinalis and quadratus lumborum, which together comprise the posterior abdominal wall. The lumbodorsal fascia originates from the spinous processes of the lumbar
vertebrae and extends anteriorly and cranially. As it progresses upward, it separates into three layers: posterior, middle, and anterior.

The **posterior layer** provides the posterior covering for the sacrospinalis muscle and is the origin of the latissimus dorsi muscle. The **middle layer** forms the fascial layer separating the anterior aspect of the sacrospinalis muscle from the posterior aspect of the quadratus lumborum. The **anterior layer** of the lumbodorsal fascia provides the anterior covering to the quadratus lumborum muscle and forms the posterior margin of the retroperitoneum. As one moves laterally away from the sacrospinalis and quadratus lumborum muscles, the lumbodorsal fascial layers fuse together and then connect with the transversus abdominis muscle.

**Gerota Fascia**

Interposed between the kidney and its surrounding structures is the perirenal or Gerota fascia. This fascial layer encompasses the perirenal fat and kidney and encloses the kidney on three sides: superiorly, medially, and laterally. Superiorly and laterally Gerota fascia is closed, but medially it extends across the midline to fuse with the contralateral side. Inferiorly, Gerota fascia is not closed and remains an open potential space. Gerota fascia serves as an anatomic barrier to the spread of malignancy and a means of containing perinephric fluid collections. Thus perinephric fluid collections can track inferiorly into the pelvis without violating Gerota fascia.
## Surgery of the Kidney

### Common surgical approaches:

<table>
<thead>
<tr>
<th>Anatomic Area</th>
<th>Incision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flank</td>
<td>Subcostal (right or left)</td>
</tr>
<tr>
<td></td>
<td>11th rib (right or left)</td>
</tr>
<tr>
<td></td>
<td>With extension to the anterior lateral (right or left) abdominal wall</td>
</tr>
<tr>
<td>Anterior abdominal</td>
<td>Subcostal, unilateral</td>
</tr>
<tr>
<td></td>
<td>Bilateral subcostal &quot;chevron&quot;</td>
</tr>
<tr>
<td></td>
<td>Midline</td>
</tr>
<tr>
<td>Combination (flank and anterior</td>
<td>Thoracoabdominal (right or left)</td>
</tr>
<tr>
<td>abdominal)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laparoscopic</td>
</tr>
<tr>
<td>Transperitoneal</td>
<td>Two 12 mm trocars in the midclavicular line, one approximately 4 cm</td>
</tr>
<tr>
<td></td>
<td>below the level of the umbilicus and the other 2 cm below the costal</td>
</tr>
<tr>
<td></td>
<td>margin. All secondary trocars placed under direct vision.</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>Three ports along the inferior border of the 12th rib: a 12 mm port</td>
</tr>
<tr>
<td></td>
<td>just posterior to the tip of the rib (superior lumbar triangle); a 12</td>
</tr>
<tr>
<td></td>
<td>mm port two finger breadths posterior to the first 12 mm port; a 5</td>
</tr>
<tr>
<td></td>
<td>mm port two finger breadths anterior to the first 12 mm port. Also, a</td>
</tr>
<tr>
<td></td>
<td>12 mm port at the inferior lumbar triangle</td>
</tr>
</tbody>
</table>
Patterns of Nephrectomy:

Simple Nephrectomy Simple nephrectomy may be accomplished by the flank approach, subcapsular technique, or transperitoneal approach. It is indicated when there is no malignant process.

Radical Nephrectomy Radical nephrectomy is the procedure of choice for renal malignancy. By definition, radical nephrectomy is the removal of the kidney, adrenal, and upper (proximal) ureter by an extrafascial en bloc resection. This is carried out together with an extended lymphadenectomy from the diaphragm above to the area below the aortic bifurcation or, if necessary, down to the pelvic diaphragm. However, radical nephrectomy performed to address Wilms tumor mass entails just lymph node sampling, as shown later in this thesis.

The major renal vessels can be visualized anteriorly by separation of the peritoneum from the anterior lamina of Gerota's fascia and posteriorly by separation of the posterior lamina of Gerota's fascia from the transversalis fascia. In other words, the major renal vessels will be found within the anterior and posterior pararenal spaces, both of which may contain malignant cells that were spread by metastasis or direct extension of the tumor.

Laparoscopic Nephrectomy is a recent innovative approach in which the kidney can be removed by laparoscopic-assisted technique. The safety and feasibility for this procedure when dealing with malignant tumors is still a debatable issue.

Nephron Sparing Surgery (NSS) is resection of part(s) or foci of one or both kidneys. When WT affects all renal units, the administration of preoperative chemotherapy enables NSS for the lesser affected side.
**Applied anatomy in relation to Nephron Sparing Surgery (NSS):**

NSS for unilateral WT is an area of current research. Though not standard of care, proper understanding of the relevant surgical anatomy is very important because it is technically more challenging than en bloc removal of the kidney by radical nephrectomy. Knowledge of the relationships of the tumor and its vascular supply to the collecting system and adjacent normal parenchyma is essential for preoperative assessment. Thus, more extensive and invasive preoperative imaging studies including arteriography and venography are sometimes necessary before NSS to delineate the intrarenal vasculature, which may aid in tumor excision while minimizing blood loss and injury to the normal adjacent parenchyma.

Advances in helical computerized tomography (CT) and computer technology now allow the production of high-quality three-dimensional (3D) images of the renal vasculature and soft tissue anatomy, and provide a topographic road map of the renal surface with multiplanar views of the intrarenal anatomy.

*Figure 4: Medial view of the disposition of the renal vasculature and its relation to the collecting system at the renal hilum (adopted from Nephron Sparing Surgery 1st ed.2008 informa healthcare)*
**Arterial anatomy relevant to NSS**

**Superior pole**

In more than 75% of cases, the superior pole is related to three arteries which can be involved in nephron sparing surgery:

1. *The superior or apical segmental artery*, which is not in close relation to the upper infundibulum and usually arises from the anterosuperior segmental artery.
2. Two other arteries, anterior and posterior, which are in close relationship to the upper infundibular surfaces, anteriorly and posteriorly.

Ligation of the superior (apical) segmental artery is easy, as its origin is quite proximal, and the artery related to the anterior surface of the upper infundibulum can also be ligated or coagulated without added care and any extra danger of extensive parenchymal injury. Management of the artery related to the posterior surface of the superior infundibulum is more complex, as risk of injury to this vessel during any partial nephrectomy procedure is associated with significant hemorrhage and infarction of about 50% of the renal parenchyma. When the anterior and posterior surfaces of the superior pole are supplied only by the polar superior artery, nephron-sparing surgery is relatively easy, because its ligation results in a clean line of demarcation making resection of the superior polar tumors a more comfortable exercise. The peripheral tumors are associated with splaying of the surrounding vessels and resection of these tumors can be achieved by careful ligation of the vessels around the tumors.

**Inferior pole**

In two-thirds of patients, the lower pole of the kidney is supplied by the inferior segmental branch of the anterior division of the main renal artery. This courses in front of the ureteropelvic junction and, on entering the
inferior pole, divides into two branches supplying the anterior and posterior surfaces. In the rest of the cases, the lower pole is supplied jointly by two arteries, a branch from the inferior segmental artery anteriorly and another from the inferior branch of the posterior segmental artery posteriorly. Ligation of both these branches during partial nephrectomy involving the lower pole tumors does not result in ischemia of the remaining parenchyma.

**Midzone**

The midzone is mainly supplied by the anterior division of the renal artery. Nephron-sparing surgery of the midzone involves infringement of the calyceal anatomy. In two-thirds of the cases, the middle group of calyces is associated with the superior and/or inferior calyceal groups and hence resection in this region should preserve adequate calyceal drainage to the remaining poles. Careful closure of calyceal ends after resection is essential to avoid postoperative urinary fistula or collection. In a third of cases, midzone calyceal drainage is independent of the superior or inferior calyceal groups and, in these cases, resection of the midzone does not present additional difficulties. Midzone tumors involve resection of the central position of the kidney while maintaining the blood supply to the remaining renal parenchyma at the poles. Technically, it is more challenging than polar nephron-sparing resections and always requires a preoperative selective renal angiogram to determine the exact intrarenal arterial anatomy and to ascertain the resectability of the lesion. Centrally-placed tumors need meticulous dissection of the arteries supplying the tumor under hypothermic and avascular control. Normal restoration of renal configuration and function can be maintained after complete resection.
**Dorsal kidney**

The posterior or dorsal part of the kidney is supplied by the posterior segmental artery, which is the first division of the main renal artery. This divides into three constant subdivisions – superior, middle and inferior, supplying the respective areas of the dorsal kidney. The middle branch sometimes interdigitates with the anterior branches supplying the midportion of the kidney. Resection of midzone tumors requires the identification and ligation of anterior branches related to the midkidney and middle subdivision of the posterior segmental artery. The tumors arising close to the hilum need careful isolation of the principal renal vessels and the renal pelvis with the upper ureter. Preliminary access to vessels is mandatory and the renal pedicle must be completely exposed and skeletonized, as midzone tumors sometimes receive secondary branches from arteries of other segments. Resection of tumors in this zone is always performed under hypothermic and ischemic control.

**Venous anatomy relevant to NSS**

Although the intrarenal veins have no segmental organization, in the majority of the cases two or three major trunks join to form the main renal vein. During partial nephrectomy, ligature of many tributaries of major trunks can be done, enabling ample exposure of the intrarenal branches of the main renal artery that usually lie in a deep plane within the renal hilum. In the presence of abundant venous collaterals, ligation of the major venous trunk is **not** associated with any infarction or loss of functioning of the renal parenchyma.
Vascular injury

During removal of left renal tumors, damage to the aorta, superior mesenteric artery (SMA), and right renal artery has been reported to occur. These vessels are in close proximity to the tumor mass, and if the aorta and IVC separate by tumor or lymphatic infiltration, they are threatened during removal of the left kidney. The left renal vein is usually identified first. Once it is divided, another artery is revealed underneath that could be the superior mesenteric artery, aorta, or left or right renal artery. This artery should not be ligated until its exact identity has been established. When in doubt, this can be done by cross-clamping the vessel with a vascular clamp. It can be clearly stated that attempts at early ligation of the hilar vessels cannot be justified until the renal vasculature is clearly identified.

The vessels most at risk during excision of right renal tumors are IVC and contralateral renal vein. In large right-sided tumors, the IVC enters the tumor mass and is hidden from vision. Under this circumstance, the right renal artery is in close proximity to the left renal vein, which can thus be damaged. If unrecognized, such damage can lead to venous infarction and loss of renal function.

Aorta and its Branches

Modern imaging techniques allow noninvasive clear outlining of the visceral blood supply. The angio-MR demonstrates the arterial branches of the aorta in a child with a left-sided WT. It shows that the coeliac trunk and SMA originate from the aorta in close proximity to the origins of the renal arteries. The distance between the origins of these aortal tributaries can be 1 cm or less.

For surgical practice it is helpful to arrange the aortic branches in the three planes they occupy as follows:
(1) blood supply to the gastrointestinal tract in front of the aorta;
(2) to three paired glands on both sides and
(3) to diaphragm and the four lumbar arteries.

Iatrogenic injury to the aorta and its branches has been inconstantly reported. These reports indicate that patients with left sided large tumors are at particular risk for this type of injury. Although attempts were always made to repair the intraoperative vascular injury, three of six patients described in literature died as a result of the vessel injury. All these children had left sided nephroblastoma; four cases had injuries to the SMA, one had both SMA and coeliac trunk, and one the aorta injury.

It has been reported that after unnoticed ligation of SMA, though the bowel may initially appear viable, full thickness necrosis develops later. When in doubt, a Doppler flow study can provide essential information. Lacerations of the SMA require surgical repair.

In contrast to SMA, dissection of the stem of inferior mesenteric artery (IMA) is commonly tolerated without disastrous consequences. Generally the marginal artery, also known as arcade of Riolan arch, (synonymously marginal artery of Drummond), sufficiently connects SMA with IMA. However, only small collaterals exist at the splenic flexure. In addition, the ascending arch of the left colic artery (AALCA) is present in at least two third of cases. This arterial branch constitutes an arch from the left transverse colon to the sigmoid colon secondary to the marginal artery.

**Diaphragmatic Injury**

Diaphragmatic injury with or without pleural involvement is an extremely rare phenomenon. The injury occurs because occasionally the posterior lamina of the Gerota's fascia is heavily fixed to the diaphragm. A tear of the diaphragm can take place when tension is applied to the fascia.
Pneumothorax Secondary to Diaphragmatic, Pleural, and Lower Lobe Lung Injuries

Any flank incision, with or without rib resection, can produce pneumothorax. The relation of the 12th rib to the transverse (horizontal) orientation of the pleural reflection should always be kept in mind.

Bleeding Secondary to Adrenal Injury

Prevention of this very common injury is imperative. The adrenal gland is a very friable organ with very rich vascularization. Venous bleeding is the result of injury of the adrenal parenchyma or its draining veins, especially the right one (which is very short, emptying directly into the inferior vena cava).

Bleeding Secondary to Splenic Injury

For left sided tumors, splenic bleeding can be massive to the extent that splenectomy becomes inevitable.

Pancreatitis and Bleeding Secondary to Pancreatic Injury

Pancreatic injuries can result in bleeding or pancreatitis. Most often they occur during left kidney surgery by elevation of the tail and distal body of the pancreas. The Kocher maneuver for mobilization of the duodenum and the head of the pancreas can produce pancreatic injury, but this is rare.

Bleeding and Bile Leak Secondary to Hepatic Injury

Peritonitis Secondary to Duodenal/Colonic Injuries
Most children with Wilms’ tumor present with an **abdominal mass** or swelling discovered by a parent or a health care practitioner, without other signs or symptoms. Other symptoms can include **abdominal pain** (30% to 40%), **hematuria** (12% to 25%), **fever**, and **hypertension** (25%).

**Hypertension** is attributed to increased rennin activity and this will usually resolve shortly after removal of the tumor. **Constitutional signs and symptoms** (e.g., weight loss, cachexia, bone pain) are unusual manifestations of Wilms’ tumor.

A subset of patients with **subcapsular hemorrhage** can present with rapid abdominal enlargement, anemia, hypertension, and sometimes fever.
Although the lung is the most common metastatic site, children rarely present with respiratory symptoms (Fernandez C et al. 2011).

The clinical presentation of abdominal pain with tumor rupture. This mimics the picture of acute abdomen and can create confusion regarding the preoperative diagnosis. In 2.5% of NWTS-3 patients, there was an erroneous diagnosis prior to surgical exploration. Most of these children did not have any preoperative imaging studies performed, and this group of patients had an increased incidence of surgical complications. This emphasizes that defining the exact histology is not as important as establishing that the child has a solid renal tumor, allowing the surgeon to plan for a major cancer operation. (Ritchey et al, 1992)

Clinical manifestations of RT sided Wilms' tumor may mimic that of acute appendicitis. Appendectomy may be done based on abdominal signs if preoperative imaging was not done. (K Burney et. al 2005)

Wilms' tumor can spread both locally and hematogenously. Local spread typically occurs into the renal hilar structures and may penetrate the renal capsule. These tumors also have a propensity to invade the renal vein and form thrombi in the inferior vena cava, sometimes progressing as far as the right atrium. Local and distant lymph node involvement can occur. The most common sites of hematogenous metastasis are the lungs and liver.

**Physical examination**

Often there is a firm, nontender, smooth mass that is eccentrically located, and rarely crosses the midline. A varicocele secondary to obstruction of the spermatic vein may be associated with the presence of a tumor thrombus in the renal vein or inferior vena cava. It is also important to note specifically any signs of the Wilms’ tumor...
associated syndromes marked by the presence of aniridia, partial or complete hemihypertrophy, and genitourinary abnormalities, such as hypospadias and cryptorchidism. (Syndromic cases) (DeVita, Lawrence and Rosenberg 2008)

It is of great impotence to examine the child gently, vigorous palpation may rupture the renal capsule, resulting in tumor spillage, which increases the tumor stage and the need for more intensive therapy.

Although Wilms' tumor is rarely diagnosed in the neonate, there are a few reported cases of prenatal detection of a renal mass with postnatal confirmation of Wilms' tumor. All of these prenatal cases were unilateral, and none was associated with multiple malformation syndrome or nephrogenic rests. One neonate presented with nonimmune hydrops with rapid growth of the tumor. (Ritchey ML et al. 1995) (Vadeyar S et al. 2000)

Patients with Wilms' tumor may also be identified through screening of high-risk patients, such as those with Beckwith-Wiedemann syndrome. However, the value of screening remains uncertain. (Scott RH et al. 2006)

**Laboratory testing**

Laboratory studies include tests for renal function including urinalysis, liver function, serum calcium, a complete blood count, and coagulation studies. Serum creatinine is obtained to detect any reduction in glomerular filtration rate prior to surgical intervention. A urinalysis is sent to detect proteinuria, a finding that can occur in patients with Denys-Drash syndrome and mesangial sclerosis. Liver function tests may be abnormal with liver metastases. (DeVita, Lawrence and Rosenberg 2008)
Elevated serum calcium can be seen in children with rhabdoid tumor of the kidney or congenital mesoblastic nephroma (Jayabose S et al. 1988)

Coagulation studies should be considered because acquired von Willebrand's disease occurs in approximately 8 percent of patients with Wilms' tumors at diagnosis. Although this abnormality usually has minimal clinical significance, there are case reports of significant bleeding requiring intensive intervention. As a result, patients should be screened for coagulopathy, and any abnormality should be corrected perioperatively. (Leung RS et al. 2004) (Baxter PA et al. 2009)
RADIOLOGICAL EVALUATION

The first goal of imaging is to establish the presence of a renal tumor. The second goal is to guide management decisions prior to confirmation of a histological diagnosis, such as surgical approach and the need for preoperative chemotherapy. Important information includes confirming the presence and function of the contralateral kidney, determining whether there is also tumor in the contralateral kidney, the size and extent of the tumor, the presence of vascular invasion and the presence of lung metastases.

Abdominal ultrasonography is the initial imaging study. It will detect hydronephrosis and multicystic kidney disease, which may present as abdominal masses or swelling. In patients with a suspected renal tumor, Doppler ultrasonography should be performed to detect tumor infiltration of the renal vein and inferior vena cava, and to assess patency of blood flow. Contrast-enhanced computed tomography (CT) is recommended to further evaluate the nature and extent of the mass. CT shows displacement of adjacent structures, rather than encasement of vessels and aortic elevation, which are characteristics that suggest neuroblastoma. CT also may detect small lesions of tumor or nephrogenic rests in the opposite kidney, which were not detected by ultrasonography.

Figure 6: CT scan view of left sided WT, it doesn’t cross the ML.
On MR imaging, Wilms' tumor is hypointense on T1- and hyperintense on T2-weighted sequences. Although MR imaging has been reported to be the most sensitive modality for determining caval patency, patients frequently require sedation during scanning. Since Wilms' tumors are often very large at presentation, severe distortion of adjacent organs, including the IVC, may prohibit a determination of venous invasion/patency. MRI is superior to other imaging modalities in delineating nephroblastomatosis lesions.

Positron emission tomography (PET) has not been shown to have any advantages over conventional imaging modalities in preoperative assessment of Wilms' tumor (Misch et al, 2008).

Regional adenopathy can be identified on CT/MRI, but enlarged retroperitoneal benign lymph nodes are common in children, and correlation between pathologic findings and lymph node evaluation at surgical exploration in Wilms' tumor patients have found significant false-positive and false-negative error rates (Othersen et al, 1990).

Imaging of the chest is needed to determine whether there are lung metastases. Although both CT and chest radiography are used to detect metastases, CT appears to be more sensitive than chest radiography. (Owens CM et al. 2002) However, there is controversy regarding the best screening modality to use for metastatic lung disease. In some institutions, CT of chest is routinely performed. An alternate approach is to use chest radiography. A patient with a normal chest radiograph is interpreted as being free of metastatic lung disease. The clinical significance of lung nodules detected on CT scan alone is controversial (Meisel et al, 1999; Owens et al, 2002). CT will clearly detect more lesions than chest x-ray (CXR), but not all of these lesions represent metastases (Ehrlich et al, 2006).

Children with genetic predisposition to Wilms' tumor should be offered screening with abdominal ultrasounds. Consideration for screening should
be performed in collaboration with a geneticist. Syndromes to consider for routine screening include WT1-associated syndromes (WAGR, Denys-Drash, and Frasier syndrome), familial Wilms' tumor, Beckwith-Wiedemann syndrome, hemihypertrophy, Simpson-Golabi-Behmel syndrome, and Perlman syndrome. Ultrasounds are recommended every 3 months until 5 to 7 years of age. Although the screening will not prevent the development of tumors, tumors may be detected at an earlier stage and reduce the potential toxicities of treatment. (Scott RH et al. 2006). Screening can be discontinued after age 7 years, since there is a significantly lower risk of developing Wilms' tumor (Beckwith 1998; Lonergan et al. 1998).

Although the vast majority of pediatric renal masses are Wilms' tumor, various other newly described lesions may have a particular clinical history or distinctive imaging features that differentiate them from Wilms' tumor. Despite the use of modern imaging techniques, renal neoplasms cannot always be diagnosed with pre-operative imaging but in the context of a clinical scenario. Malignant lesions include: Wilms' tumor, nephrogenic rests/nephroblastomatosis, clear cell sarcoma, rhabdoid tumor, renal cell carcinoma, renal medullary carcinoma, lymphoma, leukemia, and neuroblastoma. Benign lesions include: mesoblastic nephroma, ossifying renal tumor of infancy, multilocular cystic renal tumor, angiomyolipoma, and metanephric adenoma.
**Table 3** Radiological features of different pediatric renal tumors

<table>
<thead>
<tr>
<th>Renal neoplasia</th>
<th>Age range</th>
<th>Distinct clinical and imaging features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilms' tumor</td>
<td>Unilateral</td>
<td>1–11 years Most common solid renal mass of childhood. Most often large solid mass, often vascular invasion</td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>2 months to 2 years Associated with nephroblastomatosis and various syndromes</td>
</tr>
<tr>
<td>Nephroblastomatosis</td>
<td>Any age</td>
<td>Bilateral, multiple subcapsular focal masses, often with associated bilateral solid Wilms' tumors. <strong>On CT</strong> they are peripheral, hypodense, poorly enhancing nodules.</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Any age</td>
<td>Vascular encasement, stippled calcifications, neural extension</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>1 to 4 years</td>
<td>No intravascular extension, frequent skeletal metastases, sometimes difficult to be differentiated from WT</td>
</tr>
<tr>
<td>Rhabdoid tumor</td>
<td>6 months to 9 years</td>
<td>Subcapsular fluid collections, tumor lobules separated by hypodense areas of necrosis or hemorrhage, and linear calcifications outlining tumor lobules. Associated with posterior fossa cranial neoplasms</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>6 months to 60 years</td>
<td>Non-specific appearing solid renal mass with mild contrast enhancement, association with VHL</td>
</tr>
<tr>
<td>Renal medullary carcinoma</td>
<td>10–39 years</td>
<td>Small satellite nodules and caliectasis (hydronephrosis) are typical features. Exclusively seen in sickle cell trait or hemoglobin SC disease</td>
</tr>
<tr>
<td>Mesoblastic nephroma</td>
<td>&lt;1 year</td>
<td>Most common solid renal mass in infants and newborns</td>
</tr>
<tr>
<td>Ossifying renal tumor of infancy</td>
<td>6 days to 14 years</td>
<td>Calcified mass in an infant</td>
</tr>
<tr>
<td>Cystic nephroma</td>
<td>3 months to 4 years</td>
<td>Large, multicystic mass in young children</td>
</tr>
<tr>
<td>Angiomyolipoma</td>
<td>6–41 years</td>
<td>Fat and soft tissue mass associated with VHL, TS, NF</td>
</tr>
<tr>
<td>Metanephric adenoma</td>
<td>15 months to 83 years</td>
<td>Non-specific clinical or imaging features</td>
</tr>
<tr>
<td>Renal lymphoma</td>
<td></td>
<td>Diffuse infiltration, focal, or multiple masses, invasion from contiguous retroperitoneal lymphadenopathy.</td>
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DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Wilms' tumor includes neuroblastoma and other renal tumors. Clinical scenarios, imaging studies and tissue histology differentiate Wilms' tumor from these other disorders.

Neuroblastoma

Distinguishing abdominal NBL from WT is critical when evaluating children with abdominal tumors as the surgical management for these tumors differs significantly. Although surgical extirpation of the primary tumor is a critical component of the treatment of both malignancies, nephrectomy is rarely necessary in the treatment of NBL. In fact, preservation of renal function is important as increasingly nephrotoxic regimens are used to control high-risk NBL. (Shamberger RC et al. 1998). In addition, when a diagnosis of NBL is made, the optimal timing of surgery to remove the tumor is often dependent on risk stratification. In patients with high-risk NBL, initial surgery is usually limited to obtaining tissue for determining the diagnosis and tumor biology, staging, and placement of a central venous access device. Tumor resection is then performed after cytoreductive neoadjuvant therapy. (Weinstein JL et al. 2003).

In a study conducted at St. Jude Children's Research Hospital, a subset of neuroblastoma patients was originally diagnosed as WT and one of them underwent nephrectomy at the time of original laparotomy. (Paxton V. et al. 2008)

Children with NBL may present with a variety of clinical features including abdominal distension/pain, anemia, fever, weight loss, hypertension, or symptoms related to metastatic disease such as bone pain. In contrast, children with WT often only present with abdominal distension that is detected by the parents or primary care physician. Children with NBL tend
to have findings of fever and/or weight loss more frequently than children with WT (67% vs 20%).

Thus, ill-appearing children or those having a broad spectrum of constitutional symptoms during presentation for an abdominal mass should heighten suspicion for NBL. Nearly half of all patients with NBL have metastatic disease at the time of presentation, often to the bone marrow, that may lead to pancytopenia. Review of CBCs in patients diagnosed with NBL vs WT revealed that patients with NBL had lower mean white blood cell counts and lower mean platelet counts, although these children were generally not leukopenic or thrombocytopenic. (Paxton V. et al. 2008).

One staple in the diagnosis of NBL is a finding of elevated urinary catecholamines or metanephrines that will be present in more than 90% of patients. (Strenger V et al. 2007)

If there is any question as to the diagnosis, this test should be performed and the results reviewed before surgery. If urinary catecholamines or metanephrines are collected because of a questionable diagnosis of NBL, clearly, these results should be reviewed before proceeding with tumor resection and, particularly, nephrectomy.

When the diagnosis is in question, the finding of tumor calcification or vascular encasement on preoperative imaging should heighten suspicion for NBL and prompt completion of the appropriate preoperative laboratory work and staging. In cases where CT is equivocal, magnetic resonance imaging may add information with regard to the primary tumor, as well as yield staging information for both WT and NBL.

If there is still diagnostic uncertainty after completion of this workup, it is recommended that biopsy rather than resection of the primary tumor be performed so that appropriate treatment algorithms are followed. (Paxton V. et al. 2008)
Renal Cell Carcinoma

Renal cell carcinoma (RCC) is an uncommon malignant tumor of childhood. The latest (SEER) statistics indicated an incidence of 0.4 case per million persons younger than 20 years. RCC accounts for 2% to 7% of primary renal malignant tumors of childhood. The median age of children brought for evaluation of RCC is 9 years, considerably older than the age at manifestation of other pediatric renal malignant tumors. (Ries LAG et al, 2002)

Unlike with Wilms’ tumor, clear cell sarcoma of the kidney, and rhabdoid tumor of the kidney, which have been studied by the NWTS group and SIOP, no prospective clinical trials of therapy for pediatric RCC have been performed. Typical features of pediatric RCC include abdominal mass (24% to 55%), hematuria (42%), and pain (32%). Children also may exhibit the constitutional signs and symptoms of hypertension, fever, weight loss, and polycythemia. Approximately 25% of children with RCC have distant metastatic disease when they arrive for evaluation, most commonly involving the lung, liver, and bone. (Carcao MD et al. 1998)
A distinctive variant of RCC that preferentially affects children and young adults is characterized by the translocation t(X;17)(p11.2;q25), which results in a fusion product between the TFE3 and ASPL genes. This same translocation is observed in alveolar soft-part sarcoma, but it is balanced in RCC and unbalanced in alveolar soft-part sarcoma. Another variant is associated with the translocation t(6;11)(p21.1;q12). The prevalence and clinical behavior of these variants have not been characterized. (Renshaw AA et al. 1999)

Another renal epithelial malignant neoplasm of childhood is renal medullary carcinoma, which is a highly aggressive tumor associated with sickle cell trait. Categorization of pediatric RCC using the World Health Organization (WHO) classification system suggests that approximately one third of pediatric RCCs are translocation carcinomas. These tumors have distinct histological features and are associated with translocations involving the TFE3 gene at chromosomal region Xp11.2. In addition to translocation RCC, classic adult-type clear cell RCC, papillary RCC, chromophobe RCC, and oncocytic RCC associated with neuroblastoma have been described in children and young adults. (Bruder E et al. 2004)

An apparent difference between adult RCC and pediatric RCC is the prognostic significance of local lymph node involvement. Adults with RCC with lymph node involvement have a 5-year overall survival rate of approximately 20%. By contrast, a review of the published pediatric RCC experience showed that 66% of patients with local lymph node involvement without distant metastatic lesions had durable survival. (Indolfi P et al. 2003)

Clear Cell Sarcoma of the Kidney

Clear cell sarcoma of the kidney (CCSK) accounts for 3% of renal tumors reported to the NWTSG. The tumor derives its name from the clear cytoplasm of the predominant cell type (Schmidt and Beckwith, 1995).
Important predictors of improved survival are lower stage, younger age at diagnosis, treatment with doxorubicin, and absence of tumor necrosis (Argani P et al, 2000). Bilateral involvement has thus far not been reported, nor has the presence of Wilms' tumor associated congenital anomalies such as aniridia or hemihypertrophy.

**Rhabdoid Tumor of the Kidney**

Rhabdoid tumor of the kidney (RTK) is the most aggressive and lethal childhood renal tumor, which accounts for 2% of renal tumors registered to the NWTSG. RTK is now considered a sarcoma of the kidney, and the cell of origin is unknown (D'Angio et al, 1989). The tumor derives its name from the resemblance to rhabdomyoblasts, but the tumor is not derived from myogenic cells. RTK and CCSK both occur in renal and extrarenal locations, suggesting an origin from a non organspecific mesenchymal cell. Cytogenetic studies have shown that there may be a common genetic basis for renal and extrarenal rhabdoid tumors.

Typical clinical features include early age of diagnosis (median age less than 16 months), advanced stage, resistance to chemotherapy, and high mortality (Amar et al, 2001; Tomlinson et al, 2005). Younger age at diagnosis is an adverse prognostic factor. RTK is distinguished by its propensity to metastasize to the brain (D'Angio et al, 1993). In addition, RTK is associated with second primary tumors in the brain, including cerebellar medulloblastomas, pineoblastomas, neuroblastomas, and subependymal giant cell astrocytomas (Bonnin et al, 1984).

**Congenital Mesoblastic Nephroma**

Congenital mesoblastic nephroma (CMN) is the most common renal tumor in infants, with a mean age at diagnosis of 3.5 months (Howell et al, 1982; van den Heuvel- Eibrink et al, 2008). This is the most common renal
tumor diagnosed on antenatal ultrasonography (LeClair et al, 2005). Congenital mesoblastic nephroma is a very firm tumor on gross examination, and the cut surface has the yellowish-gray trabeculated appearance of a leiomyoma. There are three histological subtypes: classical, cellular, and mixed (showing areas of both classical and cellular).

The most important aspect of CMN is the usually excellent outcome with radical surgery only (Howell et al, 1982). The tumor can extend into the hilar or perirenal soft tissue, therefore complete surgical resection is important (Beckwith, 1986). Local recurrence and metastasis can occur particularly with the cellular variant of CMN (Joshi et al, 1986; Gormley et al, 1989; Fitchey et al, 2003).

**Angiomyolipoma**

Renal angiomyolipoma is a hamartomatous lesion that is only rarely seen in childhood. There is a clear association with the tuberous sclerosis complex (TSC), and presentation is more often bilateral in these patients (Blute et al, 1988; Ewalt et al, 1998). The renal lesions of the TSC include angiomyolipoma, simple cysts, polycystic kidney disease, and renal cell carcinoma. Angiomyolipoma develops in up to 80% of patients with the TSC (Ewalt et al, 1998).

The incidence of angiomyolipoma increases with age. Ewalt and colleagues (1998) reported on 60 patients with the TSC who were followed with periodic ultrasonograms. The average age at which a normal ultrasonogram became abnormal was 7.2 years. All patients with lesions greater than 4 cm in diameter were postpubertal. Annual ultrasonograms are recommended after puberty. Children with growing lesions can be managed with embolization or partial nephrectomy before they become symptomatic with bleeding (Lee et al, 1998; Williams et al, 2006).
The risk of serious bleeding appears to correlate with a diameter of greater than 4 cm (Blute et al, 1988; Dickinson et al, 1998; Steiner et al, 1993). Nephron-sparing approaches are recommended in children with the TSC, due to the presence of multiple, bilateral lesions and the risk of developing of new lesions.

**Solitary Multilocular Cyst and Cystic Partially Differentiated Nephroblastoma**

Solitary multilocular cyst, or multilocular cystic nephroma, is an uncommon, benign renal tumor. Fifty percent of multilocular cysts are found in young children, usually boys. The second peak incidence occurs in young adult women (Eble and Bonsib, 1998; Luithle et al, 2007). Although the majority of cases of multilocular cystic renal disease have been unilateral, there are rare reports of bilateral cases (Ferrer and McKenna, 1994). The gross appearance of the tumor is its most distinguishing feature. The cut surfaces reveal a well-encapsulated multilocular tumor composed of varying-sized cysts compressing the surrounding renal parenchyma. This tumor is distinguished by the finding of only mature cell types within the septa of the cyst wall. Multilocular cystic nephroma is cured by nephrectomy, but recurrence has occurred following incomplete excision by partial nephrectomy. If partial nephrectomy is considered, frozen section is indicated to exclude cystic, partially differentiated nephroblastoma (CPDN), or clear cell sarcoma, which can occasionally have a similar appearance.

Another entity reported in the literature with similar features is cystic partially differentiated nephroblastoma. The majority of these lesions occur in the first 2 years of life (Joshi and Beckwith, 1989; Blakely et al, 2003; Luithle et al, 2007).

Eble and Bonsib (1998) recommend that multilocular cystic nephroma and cystic partially differentiated nephroblastoma be considered the same entity.
They are indistinguishable radiographically. Histological examination reveals that blastemal cells or nephrogenic rests may be found in the septa of both tumors. Surgery is curative in almost all patients with recurrence, the result of incomplete resection (Eble and Bonsib, 1998; Blakely et al, 2003).

**Metanephric Adenofibroma**

Another tumor with prominent stromal features is metanephric adenofibroma. The epithelial component of these tumors can range from inactive metanephric adenoma to Wilms' tumor. Other lesions contain areas morphologically identical to papillary renal cell carcinoma. (Arroyo et al, 2000)

Metanephric adenofibromas with a composite Wilms' tumor component occur at a young age (mean of 12 months), similar to other ILNR-related Wilms' tumors that develop in patients with DDS and aniridia. None of these tumors have recurred after nephrectomy, but all have been treated with Wilms' tumor chemotherapy.
Wilms' tumor is characterized by displacement of structures, vascular invasion, and bilaterality in 10% of cases. Nephrogenic rests and nephroblastomatosis occur most often in neonates, and are distinguished by multiple, bilateral, subcapsular masses, and associated Wilms' tumors. Frequent skeletal metastases suggest clear cell sarcoma and a synchronous posterior fossa mass suggests rhabdoid tumor. Pediatric renal cell carcinoma occurs in the second decade and is associated with von Hippel-Lindau disease. Renal medullary carcinoma is a highly aggressive tumor seen exclusively in teenagers and young adults with sickle cell trait or SC disease. The appearance of renal lymphoma is variable, but most often includes multiple homogeneous masses with retroperitoneal lymphadenopathy. Leukemic infiltration of the kidneys causes bilateral reniform enlargement, although the diagnosis is usually not a dilemma based on the clinical history. Neuroblastoma is distinguished by direct extension of a retroperitoneal mass with vascular encasement and often has calcifications.

The primary differential diagnosis in a neonate with a solid renal mass is mesoblastic nephroma. Differentiation of ossifying renal tumor in infancy is possible by the presence of ossified elements. A large renal mass with multiple cysts and little solid tissue raises concern for multilocular cystic renal tumor. Angiomyolipomas contain fat and soft tissue, are often multiple and in children predominantly occur in association with tuberous sclerosis. Metanephric adenoma lacks specific features but is always well defined.
MULTIDISCIPLINARY TREATMENT

The dramatic increase in cure rate of Wilms' tumor (WT) over the past 40 years is largely a testimony to the efforts of cooperative groups consisting of oncologists, surgeons, radiation oncologists, pathologists, and statisticians. Surgery and chemotherapy are the main components of successful treatment of all cases of WT, and radiation is added for the more advanced or histologically aggressive tumors.

There are two major schools of thought in the management of WT. The Children Oncology Group (COG) that advocates upfront surgery prior to initiating treatment. On the other hand, the International Society of Pediatric Oncology (SIOP) recommends preoperative chemotherapy. Each approach has its advantages and limitations, but they have similar outcomes. Early surgery has 100% accurate diagnosis and can facilitate risk-adapted therapy. Preoperative chemotherapy (PC) can make surgery easier by inducing tumor fibrosis and reducing its volume. PC also reduces the frequency of intraoperative tumor rupture and spillage.

Patients with stage I and II disease receive two drugs, vincristine and actinomycin D, a regimen (EE-4A) that takes 18 weeks. Actinomycin D (also called dactinomycin) is given every 3 weeks. Vincristine is given weekly for 10 weeks, and then every 3 weeks until week 18. Vincristine doses are adapted for age and weight in order to avoid neurotoxicity; children rarely have alopecia from the vincristine and dactinomycin regimen. Doxorubicin is used in higher-risk patients and results in alopecia.

Radiation therapy is given to the flank or abdomen as determined by the size and histology of the original tumor, evidence of metastatic abdominal spread as seen by histological examination or diagnostic imaging studies, and tumor spill during primary resection. Care must be given to providing a uniform exposure of the vertebral column to limit scoliosis due to uneven
bone growth. A dose of 1 Gy is sufficient for local control in stage III favorable histology patients if they also received chemotherapy with vincristine, dactinomycin, and doxorubicin.

Risk adjusted therapy of unilateral WT according to the COG approach

Risk categories:

- **Very-low risk**: <2 years of age, <550 g tumour weight, stage I, any loss of heterozygosity (LOH) status
- **Low risk**: any age or tumour weight, stage I or II, but no LOH at 1p and 16q
- **Standard risk**: stage I tumours >550 g with LOH at 1p and 16q, or stage II with LOH, or stage III/IV with no LOH
- **High risk**: stage III or IV with LOH at 1p and 16q

Treatment approach:

Stage I:

- **COG very-low risk**: nephrectomy followed by observation alone is currently under evaluation; however, as per published NWTSG-5 guidelines (which are considered standard of care) these patients are treated with EE-4A regimen if they are not being treated on a study. Radiation is not recommended.
- **COG low-risk**: nephrectomy followed by postoperative chemotherapy with EE-4A regimen. Radiation is not recommended. NWTSG-5 guidelines also recommend EE-4A regimen.
- **COG standard-risk**: nephrectomy followed by postoperative chemotherapy. COG recommends vincristine, dactinomycin, and doxorubicin. However, NWTSG-5 guidelines (standard of care) recommend EE-4A regimen. Radiation is not recommended.
Stage II:

- **COG low-risk**: nephrectomy followed by postoperative chemotherapy with EE-4A regimen. NWTSG-5 guidelines (standard of care) also recommend EE-4A regimen. Radiation is not recommended.
- **COG standard-risk**: nephrectomy followed by postoperative chemotherapy. COG recommend DD-4A regimen if LOH is present; however, NWTSG-5 guidelines (standard of care) recommend EE-4A regimen. Radiation is not recommended. Increased intensity of treatment is currently under investigation.

Stage III:

- **COG standard-risk**: nephrectomy followed by postoperative chemotherapy with DD-4A regimen and abdominal/flank irradiation (under investigation). NWTSG-5 guidelines (standard of care) also recommend DD-4A regimen.
- **COG high-risk**: nephrectomy followed by postoperative chemotherapy with DD-4A regimen for 6 weeks, and then switched to regimen M (vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide), as well as abdominal/flank irradiation (under investigation). NWTSG-5 guidelines (standard of care) recommend DD-4A regimen.

Stage IV:

- **COG standard-risk**: nephrectomy followed by postoperative chemotherapy with DD-4A regimen and abdominal/flank irradiation.
- **COG high-risk (metastatic lesions with a rapid complete response at week 6)**: nephrectomy followed by postoperative chemotherapy with DD-4A regimen and abdominal/flank irradiation without bilateral pulmonary irradiation (under investigation). The latest results show that CT-only lung lesions may have improved event-free survival with chemotherapy, but do not appear to benefit from pulmonary radiation. NWTSG-5 guidelines (standard of care) also recommend DD-4A regimen.
- **COG high-risk (metastatic lesions with incomplete response at week 6)**: nephrectomy followed by postoperative chemotherapy with DD-4A regimen. If there is an incomplete/slow response of pulmonary lesions, the patient should receive whole lung irradiation and be switched to chemotherapy regimen M (approach under investigation). NWTSG-5 guidelines (standard of care) also recommend DD-4A regimen.
Some investigators have suggested that using preoperative chemotherapy (PC) may be more suitable for low-income countries, where malnourishment and late diagnosis are critical issues. However, the upfront nephrectomy (UN) approach can also be employed successfully in well-equipped centers in countries with limited resources. Thus, it seems that a more critical issue for patients with WT in these situations is tailoring the treatment to the different groups. Some pediatric surgeons felt that surgeries performed after PC were easier and the tumors felt less frail. However, this was not translated to decreased operating time or days of postoperative hospitalization. (Sultan et al. 2009)

The great successes in treating WT with favorable histology using 2 different approaches, and the scarcity of randomized studies, have kept the door open for an endless debate. Another challenge that may be faced using PC is the potential change of histology and stage causing difficulty in making accurate diagnosis and understaging. This may result in less treatment to tumors with undetectable microscopic residue in lymph nodes and perinephric fat. (Haddadin I, Hazaa I 2000)

Historically, pulmonary metastases were defined by presence of tumor on chest x-ray. The advent and improvements in CT allow for identification of much smaller lesions. The NWTSG and SIOP have both recommended treatment for tumors seen on chest x-ray but not CT, but leaving the final decision in the hands of the treating physician, making outcome measures difficult to interpret.

The role of surgery in the treatment of pulmonary relapse has been evaluated by the NWTSG in 211 patients. Although diagnostic confirmation of relapse may be required, there was no therapeutic benefit identified to the resection of a solitary pulmonary metastasis in addition to pulmonary radiotherapy and chemotherapy alone. Four-year survival rates were identical in the two groups.
The dosages and indications for radiation therapy have been optimized to decrease radiation exposure while maintaining local control and control of metastatic pulmonary lesions. The use of whole-lung irradiation (12 Gy) has been recommended for patients who present with pulmonary metastases. However, controversy remains over which patients with evidence of pulmonary metastases will benefit the most.
Multiple randomized clinical trials have been conducted by the NWTSG (now part of the COG), SIOP, and the United Kingdom Children’s Cancer Study Group (UKCCSG). The goals of these trials were: determining the appropriate role for each of the therapeutic modalities available, addressing the concerns and debates regarding the optimal treatment protocols and decreasing the intensity of therapy for most patients in an effort to prevent late sequelae of treatment while maintaining excellent overall survival. Patients were stratified into different treatment groups based on stage and pathology.

**National WT Study Group (NWTSG) and Children’s Oncology Group (COG).** The NWTSG was formed in 1969 to study WT. The early NWTSG studies, NWTS-1 (1969 to 1973) and NWTS-2 (1974 to 1978), showed that the combination of vincristine and actinomycin D was more effective than the use of either drug alone. The addition of doxorubicin (DOX) was found to improve survival for stage III and IV patients, and postoperative flank irradiation was unnecessary for stage I patients *(D’Angio et al, 1976, 1981)*.

A major achievement of the early trials was identification of prognostic factors that allowed stratification of patients into high-risk and low-risk treatment groups. Patients with positive lymph nodes and diffuse tumor spill were found to be at increased risk of abdominal relapse and therefore considered stage III and given postoperative irradiation. One of the most important findings was the identification of the unfavorable histological features that have a very adverse impact on survival.
NWTS-3 (1979 to 1986) demonstrated that stage I-II patients could be treated with 18 weeks of vincristine and actinomycin D without irradiation (D’Angio et al, 1989). For stage III FH patients, 10.8 Gy of abdominal irradiation was shown to be as effective as 20 Gy in preventing abdominal relapse if DOX was added to VCR and AMD.

NWTS-4 (1987 to 1994) proved that treatment durations of 6 months produced comparable outcomes to 15 months of therapy for patients with stages II-IV/FH tumors (Green et al, 1998). A recent analysis was done comparing the impact of postoperative irradiation on flank recurrence and survival (Breslow et al, 2006). This review found that although radiation did decrease the incidence of flank recurrence, there was no survival advantage. This was attributed to a lower post recurrence mortality in non irradiated patients.

NWTS-5 (1995 to 2003) was a single arm therapeutic trial. One of the major aims of the trial was to confirm the utility of LOH for chromosomes 16q and 1p to predict increased risk of tumor relapse and death (Grundy et al, 2005). Another objective was to evaluate the efficacy of treatment regimens for anaplastic histology WT. Stage I patients were treated with vincristine and actinomycin D, but this resulted in a low 4-year EFS of 69.5% (Dome et al, 2006). A new intensified chemotherapy regimen used for patients with stage II to IV diffuse anaplasia did not result in an improved survival.

In NWTS-5, children less than 2 years of age with stage I FH tumors and weighing less than 550 g did not receive chemotherapy after nephrectomy. This portion of the study was closed when the number of tumor relapses exceeded the limit allowed by the design of the study (Green et al, 2001a). A recent long-term review of this cohort was done comparing the outcomes to similar patients treated with postoperative AMD and VCR (Shamberger
et al, 2009). The 5-year EFS for surgery alone was 84%, but the 5-year OS was the same.

There is a trade-off between more intensive therapy and its potential long-term sequelae required for the 16% of children who relapse versus the avoidance of any postoperative chemotherapy in the majority.

A uniform approach for the treatment of tumor relapse was used in NWTS-5. These results were recently published (Green 2007). For children whose initial treatment was vincristine and actinomycin D only, there was an overall 81% survival at 4 years. Children who relapsed after initial treatment with vincristine, actinomycin D, doxorubicin, and radiation did not fare as well, with an overall 48% survival at 4 years (Malagolowkin et al, 2008).

The major conclusions derived from the National Wilms’ tumor Studies

- Routine, postoperative radiation therapy of the flank is not necessary for children with stage I/favorable histology or stage I/anaplastic tumors, or for those with stage II/favorable histology tumors when postnephrectomy combination chemotherapy consisting of vincristine and dactinomycin is administered;
- The prognosis for patients with stage III/favorable histology is optimized when the treatment program includes either dactinomycin +vincristine +doxorubicin +1,000 cGy radiation therapy to the flank, or dactinomycin +vincristine +2,000 cGy radiation therapy to the flank;
- The addition of cyclophosphamide to the combination of vincristine +dactinomycin +doxorubicin does not improve the outcome of patients with stage IV/favorable histology tumors;
- Pulse-intensive regimens maintain excellent relapse-free survival with less toxicity than previous regimens.

On the COG renal tumor protocols, there are, however, some situations where preoperative chemotherapy is recommended. These include children for whom renal-sparing surgery is planned (Blute et al, 1987), tumors are inoperable at surgical exploration (Ritchey et al, 1994), bilateral renal tumors, tumor in a horseshoe kidney, there is tumor extension into IVC above the hepatic veins (Ritchey et al, 1993b; Shamberger et al, 2001;
Szavay et al, 2004) and respiratory distress from extensive metastatic tumor.

**Inoperable Tumors.** The surgeon must make the determination that a tumor is inoperable. This decision should not be based on preoperative imaging studies, which can overestimate local tumor extension. (Vujanic et al, 2003; Reinhard et al, 2004). If the tumor is found to be unresectable, pretreatment with chemotherapy almost always reduces the bulk of the tumor and renders it resectable (Ritchey et al, 1994; Grundy et al, 2004). Patients who are staged by imaging studies alone and receive preoperative chemotherapy before nephrectomy are also at risk for understaging (Tournade et al, 1993). A patient determined to have an inoperable tumor should be considered stage III and treated accordingly (Ritchey et al, 1994).

Repeat imaging is performed after 6 weeks of chemotherapy. Experience in SIOP has shown that the majority of reduction in tumor volume occurs in the first 4 weeks (Tournade et al, 2001). After there has been adequate shrinkage of the tumor, definitive resection can generally be completed. A clinically good response (by imaging) is usually associated with a pathologically good response in terms of regressive histological changes (Zuppan et al, 1991; Weirich et al, 2001). The converse is not always true.

**International Society of Pediatric Oncology (SIOP).** In the randomized clinical trials conducted by SIOP, preoperative therapy is given before surgery. This approach usually results in tumor shrinkage, reducing the risk of intraoperative rupture or spillage (Lemerle et al, 1976). A greater number of patients have “post-chemotherapy stage I” tumors due to disappearance of micrometastases after neoadjuvant therapy. This was thought to be a significant advantage in terms of decreasing morbidity of treatment, particularly the late effects of radiotherapy.
Early SIOP studies evaluated prenephrectomy XRT (Lemerle et al, 1976). SIOP-5 (1976 to 1980) showed that 4 weeks of vincristine and actinomycin D was as effective as prenephrectomy XRT in avoiding surgical tumor rupture and increasing the proportion of patients with low-stage disease (Lemerle et al, 1983). SIOP-6, (1980 to 1987), demonstrated that patients with “postchemotherapy stage I” disease can safely be treated with 18 weeks of vincristine and actinomycin D (Tournade et al, 1993). However, patients with “postchemotherapy stage II” tumors and negative lymph nodes were found to have a higher rate of abdominal relapse if postoperative irradiation was omitted (Tournade et al, 1993). An anthracycline was subsequently added for treatment of these children. SIOP-6 confirmed the need for a three-drug chemotherapy regimen following nephrectomy for patients with “postchemotherapy stage II” lymph node-positive and stage III tumors. SIOP-9 (1987 to 1993), demonstrated that the relapse rate for stage II patients with negative lymph nodes without radiation therapy was reduced with epirubicin (Tournade et al, 2001). This study also demonstrated that treatment with vincristine and actinomycin D for 4 weeks versus 8 weeks had comparable rates of stage distribution and tumor shrinkage in patients with stage I to III disease. The majority of tumor shrinkage was noted in the first 4 weeks of therapy. Radiotherapy was limited to patients with stage II node-positive and III disease, resulting in 18% of patients being irradiated (Graf et al, 2000).

In SIOP-9, There were 59 children with stage I to IV tumors who had complete tumor necrosis induced by chemotherapy, and 98% of these children had no evidence of disease at 5 years (Boccon-Gibod L et al, 2000).

In the SIOP 93-01 (1993 to 2000), they evaluated the reduction in postoperative therapy for patients with stage I intermediate-risk and anaplastic WT (deKraker et al, 2004; Reinhard et al, 2004b). Patients
were randomized to receive either 4 or 18 weeks of postoperative chemotherapy with AMD and VCR. Two-year event-free survival (EFS) was 91.4% after 4 weeks and 88.8% after 18 weeks of therapy, demonstrating that survival can be maintained while shortening the duration of postnephrectomy therapy.

An interesting finding of the SIOP studies is the assessment of the tumor response after preoperative chemotherapy in terms of tumor volume and histology. The relative proportions of histological subtypes of WT differ following preoperative chemotherapy when compared with those reported following primary surgical resection (Weirich et al, 2001). Stromal and epithelial predominant tumors are found more often after chemotherapy. These histological subtypes may demonstrate a poor clinical response to therapy but have an excellent prognosis if the tumor is completely excised. The proportion of blastema-predominant tumors is decreased after chemotherapy, indicating some response of this tumor type to the preoperative chemotherapy. However, patients with blastema-predominant tumors after chemotherapy have a high relapse rate (Reinhard et al, 2004b). Tumor progression during therapy occurred in 5% of patients enrolled in SIOP 93-01 (Ora et al, 2007). These patients were documented to have decreased overall survival.

SIOP now classifies tumors with complete tumor necrosis following preoperative chemotherapy as “low risk.” Children with stage I “low-risk” tumors following post-chemotherapy nephrectomy receive no further chemotherapy (Boccon-Gibod et al, 2000). Tumors with diffuse anaplasia and blastemal predominance after chemotherapy are classified as “high risk,” and these children are treated with an intensified postoperative chemotherapy regimen. SIOP “intermediate-risk” tumors comprise all other histologies. (Vujanic et al, 2009).
**United Kingdom Children’s Cancer Study Group.** The UKCCSG trials use prenephrectomy chemotherapy but, unlike SIOP, they perform biopsy prior to treatment (Pritchard J et al, 1995; Mitchell et al, 2000; Pritchard-Jones et al, 2003). This is done to avoid giving chemotherapy for benign conditions, which account for 1% of lesions thought to be WT on imaging studies (Tournade et al, 2001). The other reason to perform biopsy is to avoid giving inappropriate chemotherapy to non-WTs. The UKW3 trial noted a 12% incidence of non-WTs in patients with the typical features of WT on imaging study (Vujanic et al, 2003). The UKW1 and UKW2 studies evaluated the single agent vincristine for treatment of stage I FH tumors (Pritchard et al, 1995; Mitchell et al, 2000). The overall survival of 96% compares well with two-drug chemotherapy, but age greater than 4 years was considered an adverse prognostic factor (Pritchard-Jones et al, 2003).

The UKW3 trial randomly assigned patients to either immediate surgery or to 6 weeks preoperative chemotherapy and then delayed surgery. Event-free and overall survival at 5 years was similar in the two groups. Around 20% of survivors avoided treatment with doxorubicin or radiotherapy, due to favorable stage distribution after preoperative therapy. They concluded, like the SIOP group, that all children with nonmetastatic WT should receive chemotherapy prior to tumor resection. (Mitchell et al. 2006)
SURGICAL CONSIDERATIONS

The initial therapy for most children with WT is radical nephrectomy through a transperitoneal (either subcostal or transverse upper abdominal incision) approach. Despite the presentation of most Wilms' tumors as a large mass, resection is generally feasible. WT, in contrast with neuroblastoma, is much less likely to invade surrounding organs and lymph nodes, which complicates the resection.

There are several important considerations to keep in mind when performing operations on children with WT. The first is to do a safe operation without unnecessary extensive resections. The second is to thoroughly understand what constitutes a complete procedure. Third, the surgeon plays an important role in accurately staging the disease, which is essential to tailor the adjuvant therapy.

Intraoperative events that negatively affect patient survival include tumor spill, deficient operations (i.e., failure to sample regional lymph nodes), incomplete tumor removal, not assessing for extrarenal tumor extension, and surgical complications. *(Kieran & Ehrlich 2015)*

Thorough exploration of the abdominal cavity is necessary to exclude local tumor extension, liver and nodal metastases, or peritoneal seeding. Biopsy is performed on suspicious lesions.

Exploration of the contralateral kidney is no longer mandated prior to nephrectomy if the preoperative CT or MRI demonstrates a normal kidney *(Ritchey et al, 2005)*. The renal vein and IVC are palpated to exclude intravascular tumor extension prior to vessel ligation.

WT extends into the inferior vena cava in approximately 6% of cases and may be clinically asymptomatic in more than 50% *(Ritchey et al, 1988; Shamberger et al, 2001)*.

Selective sampling of suspicious nodes is an essential component of local tumor staging. Formal retroperitoneal lymph node dissection is not
recommended (Othersen et al, 1990; Shamberger et al, 1999). Extensive lymph node dissection, particularly above the renal hilum, can result in chylous ascites (Weiser et al, 2003).

A major responsibility when performing a nephrectomy for WT is **complete removal of the tumor without contamination of the operative field.** Gentle handling of the tumor throughout the procedure is mandatory to avoid tumor spillage, because these patients have a six fold increase in local abdominal relapse (Shamberger et al, 1999).

Risk factors for local tumor recurrence relevant to the surgical procedure include: **tumor spillage, incomplete tumor removal, and absence of any lymph node sampling.** The 2-year survival after abdominal recurrence was 43%, emphasizing the importance of a careful and complete tumor resection (Shamberger et al. 1999).

**Surgical Principles and Techniques**

**General principles:**

- **Abdominal Block:** using the maneuver of **TAP** (transversus abdominis plane) block, to block the sensory nerves of the anterior abdominal wall is a good practice for the sake of proper post operative analgesia. It is done either by blind technique or by U/S guidance. The aim is to place a large volume of local anaesthetic in the fascial plane between the internal oblique and transversus abdominis which contains the nerves from T7 to L11. The onset of the sensory block appears to be relatively slow, taking up to 60 min to reach the maximal effect, so ideally the block is placed at the start of surgery to give adequate time for the onset of sensory analgesia. (McDonnell JG et al. 2007). Routine use of TAP in pediatric surgery, as
a part of multimodal analgesia has been pursued in many centers and proved to an effective alternative to epidural anaesthesia. (Galante D et al. 2012)

- Complete abdominal exploration.
- A unilateral radical nephrectomy with lymph node sampling via a transperitoneal approach is the surgical procedure. Flank incisions should not be utilized (limited exposure).
- Palpate renal vein and IVC for extension.
- Avoid rupture or spillage by use of an adequate abdominal or thoracoabdominal incision. **Do not biopsy the tumor.**
- Ureter is ligated and divided as low as conveniently possible.
- Titanium clips used to identify residual tumor.
- Lymph node sampling should include renal hilar and paraaortic, and/or paracaval nodes as well as any additional suspicious nodes.
- For tumors deemed inoperable at surgical exploration, open biopsy is obtained.

![Figure 8: Routine immediately pre-incision U/S guided TAP blockade is an adjunct tool to post operative analgesia. (A case of WT in our series)](image-url)
RESPONSIBILITIES of the SURGEON

Dictated Operative Report including:

- Demographics (name, date, surgeon, preoperative diagnosis, postoperative diagnosis, operation)
- Clinical Summary (age, sex, symptoms and brief outline, preoperative treatments, indications and objectives of surgery)
- Operation-narrative summary (incision, general observations, description of procedure, extent of spread, placement of clips, presence of gross tumor residual, all specimens taken, staging biopsies, and blood loss)

Tumors should be considered unresectable if:

- There is extension of tumor thrombus above the level of the hepatic veins. These patients should be considered for tumor resection when there is evidence of regression of the vena caval thrombus regardless of the degree of response of the primary tumor.

- The tumor involves contiguous structures whereby the only means of removing the kidney tumor requires removal of the other structure (e.g. spleen, pancreas, colon but excluding the adrenal gland). Note however, that Wilms' tumors are frequently adherent to adjacent organs. In the majority of cases, there is no frank invasion by the tumor and the organs can be dissected freely from the tumor.

- Radical en bloc resection, e.g. partial hepatectomy is not generally warranted. If however, removal of a small section of diaphragm, psoas muscle, or tip of the pancreas allows the tumor to be removed intact, this is considered appropriate.

- If it is the surgeons’ judgment that nephrectomy would result in significant or unnecessary morbidity/mortality, diffuse tumor spill, or residual tumor.

- If there is pulmonary compromise due to extensive pulmonary metastases.
Operative Procedure’s highlights

Full abdominal exploration through a generous transabdominal, transperitoneal or thoracoabdominal incision is recommended for adequate exposure. For very large tumors or those that come off the superior pole and extend up to the diaphragm, a thoracic extension of the incision through the eighth or ninth rib helps with exposure. (K Kieran et al 2015). Struggling through an inadequate incision will often result in rupture of the tumor, both increasing the stage of the tumor and the risk for intra-abdominal recurrence. (Shamberger et al. 1999)

If the imaging studies are suggestive of a possible lesion on the contralateral kidney, the contralateral kidney should be formally explored to rule out bilateral involvement. This should be done prior to nephrectomy to exclude bilateral Wilms' tumor. To do this exploration adequately, the colon and its mesentery should be mobilized from the anterior surface of the contralateral kidney, Gerota's fascia incised, and the kidney turned forward to palpate and visualize both its anterior and posterior surfaces. Any areas suggestive of bilateral involvement should be biopsied.

► The lateral peritoneal reflection is opened, and the colon is reflected medially. A plane is established outside of Gerota's fascia by sharp and blunt dissection. Before mobilizing the primary tumor, an attempt should be made to dissect, expose and ligate the renal vessels in order to lessen the chance of hematogenous spread of tumor cells while removing the tumor. Early ligation of the vascular pedicle is ideal; however, WTs can be very large, and it may not be possible or safe to ligate the vessels at first. WTs can be hypervascular and have large areas of necrosis that may predispose to rupture; thus, careful handling of the tumor is needed. (Gow et al. 2013).

Preliminary ligation should not be pursued if technically difficult or dangerous since premature attempts at vascular control, particularly of left
sided tumors, may result in ligation of the superior mesenteric artery (Ritchey ML et al, 1992)

Gross hematuria in children with Wilms’ tumor is infrequent, but its occurrence suggests extensive involvement of the renal pelvis with possible extension into the ureter. Cystoscopy should be considered in these children to identify extension of the tumor into the bladder and to avoid transection of the tumor thrombus during division of the ureter. Ureteral extension that is entirely resected does not increase the local stage of the tumor.

If the tumor involves the upper pole, the adrenal gland is generally resected to achieve adequate margins around the tumor and also to obtain periaortc or pericaval lymph node tissue. In children with lower pole lesions, the adrenal gland may be preserved. Ipsilateral adrenalectomy was once considered a component of radical nephrectomy. However, the need for routine resection of the adrenal gland has been reconsidered in both adult and pediatric renal neoplasms. A review of nephrectomy for nonmetastatic disease in NWTS-4 and NWTS-5 found adrenal involvement in 4.4% of patients, but similar overall and event-free survival (EFS) in patients who had undergone adrenalectomy or adrenal preservation. There were no cases of adrenal insufficiency in any child with a unilateral WT. Other reports support these observations. The current recommendation is that the adrenal gland should remain in situ if possible, but not at the risk of rupturing the tumor. (Moore K et al, 2010) (Kieran et al. 2013) (Kieran & Ehrlich 2015)

The ureter is ligated and divided as low as conveniently possible, but it is not necessary to remove the ureter completely. As the tumor is mobilized the ureter is divided close to the bladder to avoid creating a “diverticulum” on the bladder which might produce recurrent urinary tract infection. This will also assure that any extension of tumor into the ureter is entirely resected.
The tumor and the uninvolved portion of the kidney are mobilized and removed intact. Any enlarged or suspicious lymph nodes should be included with the specimen. Any suspicious areas that represent metastases should be biopsied, the site(s) identified with small titanium clips so that the locations can be determined later by roentgenograms. The involved areas should be drawn on the diagram in the surgical checklist. The specimen should be specifically identified as to the site from which it was removed. The use of titanium clips is strongly recommended to identify gross residual tumor. Clips should not be used for hemostasis and those placed for X-ray identification or radiation therapy portals should be limited to the minimum number necessary. Metallic clips can interfere with the CT scan. Clips are best applied by placing a non-absorbable suture in the structure to be marked, and attaching the clip to the suture. In general four small clips should be sufficient to delineate the margins of the tumor.

Figure 9: Careful handling of the huge, heavy mass with early vascular control is an important step preventing the grave complications of intraoperative spillage.

**Lymph Node Documentation**

Studies have demonstrated that the surgeon’s gross inspection and assessment of lymph nodes does not reliably correspond with the pathologic involvement of tumor with false-negative and false-positive rates of 31.3% and 18.1%, respectively *(Othersen HB Jr. et al 1990)*
The presence or absence of disease in hilar and regional lymph nodes is an extremely important factor in appropriate treatment. Routine lymph node sampling from the renal hilum and the paracaval or paraaortic areas must be done to guide adequate therapy. Involved or suspicious lymph nodes should be excised. Formal lymph node dissection is not recommended. Once the tumor is removed, lymph node sampling is required. Visual inspection and radiographic determination of nodal status has poor sensitivity and specificity. Lymph nodes should be sampled from the renal hilum and great vessels. Although there are no formal recommendations for the number of lymph nodes to sample, recent retrospective data suggest that a minimum of 7 increases the chances of detecting a metastasis. Failure to sample lymph nodes is the most common error made by surgeons. Lymph node status is important for staging, therapy, and long-term outcome. Failure to sample lymph nodes may result in understaging and increase the risk of recurrence and a poor outcome. (Kieran et al. 2012) (Ehrlich PF et al, 2013)

Renal Vein/Inferior Vena Cava
Intraoperatively, the renal vein should always be palpated to ensure it does not contain tumor. Transesophageal echocardiography may also be used to assess the extent of the thrombus preoperatively and to monitor the thrombus in real time during the surgery. Oncologic outcomes are equivalent when a tumor thrombus is resected upfront or after neoadjuvant chemotherapy. However, there is a significantly lower serious complication rate in children whose tumors are at or above the hepatic cava who are treated first with chemotherapy. In NWTS-4, complications were associated with both the extent of tumor (36.7% in children with atrial extension compared with 17.3% for children with IVC extension) and the initial therapeutic modality (26.0% for children with upfront resection compared
with 13.2% or children receiving preoperative chemotherapy). Current COG protocols recommend primary resection only when the distal extent of the thrombus is at or below the infrahepatic cava. Upfront chemotherapy is generally associated with excellent tumor response that may obviate the need for cardiopulmonary bypass to achieve complete resection of the intravascular tumor, but the likelihood of response is associated with the initial extent of the tumor: in NWTS-4, tumor shrinkage occurred in 86.5% of patients with tumor limited to the IVC but in only 58.3% of patients with tumor extending into the right atrium. Tumor progression despite chemotherapy may occur, and so, careful preoperative and intraoperative monitoring of these patients is mandatory. Intraoperative management of a tumor thrombus requires proximal and distal vascular control. Intraoperative US may be useful to identify the extent of the tumor if this cannot be definitively identified by palpation. Hepatic mobilization or cardiopulmonary bypass or both may be needed for extensive tumor thrombus that persists despite upfront chemotherapy. In most cases, the tumor thrombus can gently be milked out of the affected vein, although extensive thrombus may be best managed with a venotomy to facilitate thrombus mobilization. In some cases, the thrombus is attached to the intimal layer of the vein; when this occurs, the surgeon should note this in the operative report and resect the tumor using curettage in a manner similar to that used for carotid endarterectomy. Every effort should be made to resect the tumor thrombus in continuity with the primary tumor, as division of the thrombus is associated with an increased stage of disease and more adjuvant therapy. (Nakayama DK et al, 1986) (Poortmans G et al, 2001) (Shamberger RC et al, 2001)
Primary resection of tumors with extension into the inferior vena cava above the level of the hepatic vein or into the atrium is associated with higher operative morbidity. In these circumstances, preoperative chemotherapy decreases the size and extent of the tumor thrombus without increasing its adherence to the vascular wall, thereby facilitating subsequent excision. Ultrasonographic studies are essential to identify vascular extent of the tumor. A prospective study from the COG found that CT was equal to Doppler US in detecting vascular tumor extension. (Khanna G et al, 2012)

The tumor that extends into the renal vein and cava and is “free floating” can usually be simply extracted intact with the kidney specimen. In most cases, the tumor thrombus can gently be milked out of the affected vein, although extensive thrombus may be best managed with a venotomy to facilitate thrombus mobilization. (Kieran K et al, 2015). Control of the renal vein and caval above and below the tumor with vessel loops is necessary. The tumor should not be transected. Silk 2-0 stitches can then be placed on either side of the renal vein. This will help with vascular control and limit bleeding. The tumor and kidney should be completely mobilized prior to removing vascular thrombus. A venotomy is then done and the tumor pulled out of the vein. A Foley balloon technique can also be used to

Figure 10: CAVOTOMY with extraction of malignant thrombus. In this case of our series, the thrombus isn’t adherent to the intima of the IVC.
pull out the tumor. In other instances the tumor may be fixed to the vascular lumen. Extraction is more difficult and a larger venotomy may be required. A similar technique used for removing plaque for a carotid endarterectomy is helpful to lift the tumor off the vein wall. If after preoperative chemotherapy the tumor still extends above the hepatic veins, cardiopulmonary bypass is needed to remove the vascular extent of the tumor. The abdominal tumor is mobilized and removed first prior to administration of heparin. After placing the child on bypass the right atrium is opened and the tricuspid value inspected. The tumor is removed from the heart above and the below at the same time to prevent tumor emboli.

**Tumor Biopsy, Spills and Ruptures**

**BIOPSY**

Studies have shown a higher risk of recurrence in patients who had tumor spills or ruptures irrespective of the cause or extent of the soiling. These events result in an increased risk of local recurrence and increased adjuvant therapy with its attendant risks. **Tumor biopsy prior to nephrectomy is considered local spill.** This results in children receiving additional chemotherapy (doxorubicin) and radiation therapy. The low rate of misdiagnosis, the manageable short-term toxicity associated with the WT drugs, and the lack of known long-term effects suggest that with modern imaging techniques, prechemotherapy biopsies may not be necessary. *(Hall et al. 2006)*

**TUMOR SPILLAGE**

It is important for accurate staging to document the extent of any peritoneal soilage by tumor so that the prognostic implications of any such event can be studied. The stage will also determine the need for radiation therapy. "Spillage" refers to transgression of the tumor capsule during operative removal whether accidental, unavoidable or by design. Tumor tissue may be
cut across during removal of adherent structures or during removal of lymph nodes. The surgeon should indicate whether the peritoneal cavity was soiled by tumor cells, either locally or diffusely during this removal. Tumors and adherent tissues that are removed en bloc should produce no tumor spill. Those that are removed as separate specimens, the neoplastic tissue having been cut across in the process, shall be considered to be spilled (local or diffuse). Spill would occur if the surgeon transected the renal vein or ureter at the site of tumor extension. When tumor extends into the renal vein or inferior vena cava, a precise description of the technique of removal should be given in the operative note. It must be stated in the operative report if the intravascular tumor extension was removed en bloc or if tumor was transected as well as if the tumor thrombus is removed completely and if there is evidence of either adherence or invasion of the vein wall. Preoperative and intraoperative biopsies are contraindicated and should only be performed when a tumor is deemed inoperable. Preoperative percutaneous needle biopsy from the anterior or posterior approach shall be considered "local spillage". Open incisional biopsy prior to nephrectomy shall be considered a local spill unless, in the surgeon's judgment, the whole peritoneal cavity has been soiled in the process. The technique and timing of biopsy should be described fully in the operative note to assist reviewers in assessing the prognostic impact of such biopsies. It is important to note that spill results in an increased risk of local recurrence and that diffuse spills require increased adjuvant therapy with the attendant risks.

**Rupture** refers to either the spontaneous or post-traumatic rupture of the tumor preoperatively with the result that tumor cells are disseminated throughout the peritoneal cavity. Intraoperative tumor rupture occurs in approximately 9% of procedures and is associated with tumors more than 15 cm. *(Gow et al. 2013)*. Most tumor ruptures occur during mobilization of
the posterior aspect of the tumor where it is adherent to the diaphragm. An adequate incision and resection of a segment of the adherent diaphragm can often prevent rupture. Bloody peritoneal fluid shall be considered a sign of major soilage, whether or not gross or microscopic tumor is identified in the fluid. There are times when the tumor may rupture posteriorly and the perforation is confined to the retroperitoneal space, thus qualifying as local soilage. When a hematoma is present, it is assumed that tumor cells will spread with the blood. Staging of such patients is problematic. The superior, inferior, medial and lateral margins of the associated hematoma should be described fully in the operative note, and the margins marked with titanium clips. Tumor may penetrate the kidney capsule, and the overlying peritoneum, the raw neoplastic tissue surface being in free communication with the peritoneal cavity. This shall be considered major soilage. Separate, distinct nodules of tumor on the peritoneal or serosal surfaces, at a distance from the primary neoplasm ("satellite implants") shall be considered a sign of major soilage.

Complete description of all techniques is essential. Local spills are defined as those limited to the renal fossa. Diffuse spills are those occurring beyond these limits.

**Surgical Specimens**

All surgical specimens removed should be presented to the pathologist fresh or in saline, rather than fixed in formalin. Specimens should be transported to pathology immediately after removal to allow sampling of fresh tissue for molecular and biology studies. Notification of the pathology laboratory in advance will facilitate proper specimen collections. Specific labeling and adequate identification of each specimen removed is most important.
Most unilateral WT s are not amenable to NSS. However, improved imaging, anesthesia and surgical techniques have prompted some surgeons to consider NSS surgery in children with unilateral WT s. This is a highly controversial topic in the treatment of children with WT s. The question is not whether NSS is technically possible, but it is whether it provides any benefit or harm. A single-institution retro- spective review of the experience with unilateral WT s after upfront chemotherapy found no deaths and no recurrences after 6 years (Zani A et al, 2005).

In the SIOP 2001 protocol, although not formally recommended, the guidelines were available in the protocol. Upfront chemotherapy was administered for 4 weeks. Successful NSS was performed in only 3% of patients, and negative margins were achieved in only one third of patients. More importantly, in the stage 3 group, 58% had stage 3 disease because of
positive margins. These patients received extrachemotherapy and radiotherapy that they would not have had if a nephrectomy were performed. EFS was slightly higher in this group, but short-term overall survival was equivalent to that of those undergoing complete nephrectomy. In the recent COG ARENO3B2 study, unilateral partial nephrectomy for children with 2 healthy kidneys is not endorsed. Ferrer et al. looked at the feasibility of performing partial nephrectomy in children in the ARENO532 very-low-risk study, and similar to the SIOP data, they found that only 9% of these children would have met the criteria. (Ferraro FA et al, 2013). The most common reason that tumors were not considered amenable to NSS was location of the tumor relative to vascular structures; as NSS is typically performed after upfront chemotherapy, the proportion of children eligible for NSS may increase if neoadjuvant therapy were administered, but the risks of additional chemotherapy in this population must be considered, particularly in light of the already-excellent clinical results achieved using current surgical techniques.

There are several facts to consider when interpreting these reports. First, these all reflect a highly selected group of patients without standing expected EFS and overall survival. Second, WTs start from Nephrogenic rests and are often multifocal in nature. Therefore, one could be leaving behind premalignant cells that could clonally expand overtime. Third, although 5-year survival rates are equivocal, it is unclear that this is the optimal outcome standard. As mentioned, these children are expected to have excellent long-term survival and their health problems come later in life. The theoretical advantage of preserving renal units is that doing so decreases the risk of renal failure and hypertension. Long-term outcomes studies in this population show the major risk factor for renal failure is flank/whole abdomen radiation and not loss of renal tissue (Green DM et al, 2013). In fact, the renal failure rate in children with non syndromic unilateral WT at
50 years of age is lower than the renal failure rate in the American population. Hypertension is also due to radiation exposure and not due to renal failure. In summary, few patients with unilateral WT would be eligible for NSS, and many of them may end up having positive margins. Although the data for short-term survival are equivocal in these small studies, there is significant risk of exposure to well-recognized long-term toxicity. Consideration of performing NSS in a child with unilateral WT should be carefully thought out and possibly only performed in conjunction with a clinical trial. (Kieran K et al, 2015)

The COG has proposed a renal-sparing protocol for select patients with unilateral WTs. These include patients known to be at risk for bilateral disease or those at increased risk for renal failure. These patients will be managed with a strict surgical protocol to minimize risk for residual disease (Cozzi et al, 2004). The lesion should be completely excised with a margin of normal renal parenchyma. These patients should not undergo partial nephrectomy if the tumor cannot be removed as a stage I entity. Patients with high-risk histological patterns, such as anaplasia or persistent blastema-predominant tumor after chemotherapy, should be treated with complete nephrectomy because these tumors have resistance to chemotherapy.
The role of minimally invasive surgery for WT has been evaluated in different studies. It should be based on accepted oncologic principles. First, laparoscopic nephroureterectomy should effectively accomplish all of the steps achieved by an open approach. Second, the operation must allow for an adequate oncologic procedure: the operation must minimize the risk of tumor rupture, allow adequate visualization of tumor and metastases to maximize reduction of tumor burden, and provide a means to further stage the disease. Finally, it is important to consider the use of a slightly larger incision to remove the tumor in an oncologically sound manner. A considerable debate remains as to which patients will benefit from this procedure. (Patrick J. Javid et al 2011)

Recently, small case series have demonstrated the safety and feasibility of a laparoscopic approach to Wilms' tumor (Barber TD et al, 2009). There have been no reported complications, and tumor rupture has not occurred. In addition, there are preliminary but encouraging data that a laparoscopic approach to nephrectomy in benign disease is associated with decreased lengths of stay and analgesic requirements in the pediatric patient (Kim C et al, 2009).

In the child with cancer, there is an added theoretical benefit in that a laparoscopic approach may hasten recovery and thereby reduce the time required to begin or reinstitute chemo- or radiotherapy postoperatively. Some authors recommend the use of a laparoscopic approach in children with favorable histology Wilms' tumor that is not locally advanced or metastatic (Durate RJ et al, 2006).

A more rigorous study on a multi-institutional level of the safety and long-term outcomes of laparoscopic nephroureterectomy for Wilms' tumor is
required to best determine the appropriate indications for this operation. (Patrick J. Javid et al 2011).

Minimally invasive NSS for unilateral WT

Although the use of MIS for NSS has been well described for benign conditions in children, such approach for malignant tumor also remains controversial. In the adult population, laparoscopic NSS has been demonstrated to be safe with benefits in terms of recovery time and postoperative complications in the treatment of early renal cancer. (Gong EM et al, 2008)

Reports of MIS for NSS in cases of pediatric-localized WT are scant despite the fact that interest for MIS in the treatment of pediatric cancer has been growing. This is probably because, even in the context of screening programs, surgeons rarely face tumors whose location and size make MIS for NSS safely feasible. Potential disadvantages of MIS for WT are a small working space with the consequent need for advanced surgical skills and concerns regarding tumor spill, peritoneal and port site recurrence. (Nelson P et al 2012)

Only small tumors relative to the kidney and patient size and noncentral tumors can be considered for this approach. Ideally, selected tumor must be responsive to neoadjuvant chemotherapy. Selected patients must be treated at facilities where surgeons are experts in surgical oncology and MIS.

Nelson P et al published a case report where minimally invasive NSS was adopted for unilateral WT, from retroperitoneal approach. The patient was 25 months old, diagnosed with WT on top of BWS. She also received preoperative chemotherapy. They concluded that NSS can be adopted in
selected cases of small stage 1 WT treated with neoadjuvant chemotherapy when performed by an experienced team.

**Surgical Management of Metastases**

**Intra-abdominal Metastases**
Any suspicious site in the abdomen or liver should be biopsied or resected at exploration to determine the nature of the mass as it will affect tumor stage and therapy. If residual intra-abdominal metastatic disease remains at Week 12 of chemotherapy, it should be resected if complete resection is feasible. If complete resection is not feasible, then residual disease should be reassessed for feasibility of resection at the completion of therapy.

**Pulmonary Metastases**
It is strongly recommended that if there is any doubt about the nature of pulmonary nodules that these be biopsied since as many as one third of small (<1 cm) lesions may not be metastatic tumor. All very low risk patients with pulmonary lesions at relapse will receive whole lung radiation. Thus it is critical to define the nature of small pulmonary lesions at relapse. Most metastases are peripheral and superficial and can be removed thorascopically. For larger lesion (e.g. right middle lobe mass) or for those wishing to perform an open procedure, a standard posterior lateral thoracotomy incision for exploration of the chest can be used. If pulmonary nodules remain after Week 12 of chemotherapy (and irradiation), they should be resected if complete resection is feasible. If complete resection is not feasible, then imaging studies should be repeated at the end of protocol therapy to reassess for feasibility of resection. *(Green DM et al. 1991)*
Gregory and colleagues studied the two different treatment approaches in 114 patients and found no statistically significant differences in local relapse rates between them. Two risk factors related to local recurrence that have been identified as being directly related to technical aspects of the surgical resection are intraoperative tumor spill and positive surgical resection margins. (Hall G et al 2006)

Other surgical problems may affect outcome by delaying the start of postoperative therapy. An early NWTS study suggested that delay in starting radiation therapy by more than 10 days adversely affected outcome, although this has been disputed in a more recent study of 1226 children enrolled on NWTS-3 and NWTS-4. These studies found the 8-year abdominal recurrence rate to be 4.8% and 5.3%, respectively. (Neville HL et al, 2000) (Kalapurkal AJ et al, 2003)
COMPLICATIONS

Because of the high curability and excellent prognosis of Wilms' tumor, all efforts of clinical trials have been directed to avoiding the complications and long-term side effects of different modes of therapy.

From the surgical standpoint, complications can be categorized as follows

**Intraoperative complications**

- Intraoperative spill
- Anatomic complications of surgery (nephrectomy): extensive hemorrhage, vascular & organ injuries. (see surgical anatomy section)

**Post-operative complications**

- Early (within 30 days post operative): Intestinal obstruction, surgical site infection (SSI), chylous ascites, and pulmonary complications.
- Delayed (beyond 30 days): Incisional hernia, complications of MIS (peritoneal metastases & port site recurrence)

Summary of complications reported in collaborative studies and large series

Children undergoing initial nephrectomy in a **NWTS-3 study published in 1992** demonstrated a complication rate of **19.8%** in a group that was very closely followed. The most frequent complication was **intestinal obstruction** occurring in **6.9%** of the children followed by **extensive intraoperative hemorrhage** (>50 ml/kg of body weight) occurring in **5.8%**. **Injuries to other visceral organs** (1%) and **extensive vascular injuries** (1.4%) were much less frequent. **Nine deaths** were attributed to surgical complications (0.5%), only one of which was intraoperative. The **factors** which were associated
with an increased risk of surgical complications were advanced-stage local disease, intravascular extension of the tumor, and resection of other organs. (Ritchey ML et al, 1992) (Ritchey ML et al, 1993)

Complications in the NWTS-4 study have also been assessed. Surgeons were discouraged from performing extensive operations on children in this study involving resection of adjacent organs or massive tumors. Complications occurred in 12.7% of a random sample of 534 of the 3,335 patients treated on this study. Again, intestinal obstruction was the most frequent complication (5.1%) followed by extensive hemorrhage (1.9%), wound infection (1.9%), and vascular injury (1.5%). The factors associated with an increased risk of complications were again assessed. Intravascular extension into the inferior vena cava or atrium and nephrectomy performed through a flank or paramedian incision were both significant factors. Tumor diameter greater or equal to 10 cm was also associated with increased complications. Finally, the risk of complications was increased if the resection was performed by a general surgeon rather than a pediatric surgeon or pediatric urologist. (Ritchey ML et al, 2001)

SIOP reported a complication rate of 8% in a study involving 598 patients registered on SIOP-9. These patients were pretreated with vincristine, dactinomycin and epirubicine or doxorubicin prior to nephrectomy. The most frequent events were small bowel obstruction (3.7%) and tumor ruptures (2.8%). The latter is not reported as a complication in the NWTS reviews. Other complications occurred in 2.0% of patients. (Godzinski J 1998).

In their institution experience, Hall G et al. evaluated the surgical outcome in 160 cases that had undergone radical nephrectomy (RN) for
WT, of which 114 had preoperative chemotherapy (PC) and 46 had upfront nephrectomy (UN). They found that tumor spill occurred in 6 (5.3%) of 114 PC and 2 (4.3%) of 46 UN patients. In their study, tumor inhomogeneity, tumor size, and inferior vena cava compression/clot at diagnosis did not affect incidence of spill. Of 6 PC patients with surgical spill, 1 (17%) had significant tumor shrinkage, compared with 87 (81%) of 108 without spill. Other surgical complications included bowel obstruction {PC 5(4.4%) – UN 3(6.5%)}, Intussusception {PC (1.8%) – UN 1(2%)}, wound infection {PC 3(2.6%) – UN 1(2%)}, spleno-renal ligament tear {PC 1(0.8%) – UN 0}, hepatic vein tear {PC 1(0.8%) – UN 0}, post surgical IVC clot {PC 0 – UN 1(2%)}. They concluded that surgical complication rates in the PC were 14% compared with 17% in the group that had primary resection. Thus, PC neither increased nor decreased the surgical morbidity. (Hall G et al, 2006)

This complication can occur at different times; preoperative rupture (spontaneous or traumatic), biopsy (needle or open), or during surgery from either the tumor (rupture of capsule or removal of the tumor in more than one piece) or by transection of involved structures (lymph nodes, vein, or ureter).

A report from the COG addressed the event of intraoperative spill (IOS) and identified two distinct sites of origin of IOS: the primary tumor and tumor thrombus spilling from veins. Spill from the primary tumor alone was (9.7%), renal vein alone (1.8%), and both (0.4%). Altogether the overall rate of IOS was 11.9%. (Kenneth W. Gow et al, 2013)

Two important tumor characteristics that guide surgeon decision-making include size and location. In NWTS-4, a tumor diameter ≥10 cm was associated with an increased risk of complications (Ritchey ML. et al,
In the report from COG, the incidence of IOS became significant with tumor diameter measuring 12 cm and peaked at 15 cm. It is likely that it is this size range in which great care must be exercised during primary tumor resection. The implication is that size may be related to a more challenging operation; limited operative field, distorted normal anatomy, difficult dissection from surrounding structures, more difficult to handle the tumor, difficult isolation of renal vasculature, and thinner tumor capsule due to outgrowing blood supply. (Kenneth W. Gow et al, 2013). A single institution study showed that tumor volume calculated by CT scan of greater than 1000 cc to be at higher risk of IOS (Barber TD et al, 2011). Right-sided tumors were also identified as a risk factor for IOS. There are anatomic differences between the two sides which may explain this finding. The right kidney is in close proximity to the liver, which results in less space for dissection when compared to the left upper abdomen. Further, there are anatomic differences in the renal vasculature, which may make for more difficult dissection for right-sided lesion, especially if the tumor is obscuring visualization. There are more congenital anomalous variants of the right renal arteries, and veins as compared to the left sided vessels and veins. Also, due to the close proximity of the right renal vein to the IVC, it is about half the length compared to the left renal vein. When these differences in vasculature are considered together, the risk of an inadvertent tumor spill is higher on the right. (Katkoori D et al, 2009)

One of the main pros of (SIOP) approach is to reduce IOS is through prenephrectomy chemotherapy. The published SIOP studies have reported a lower intraoperative tumor spill rate of 2.8–6%. It is believed that primary chemotherapy makes subsequent surgical extirpation easier due to significant tumor shrinkage and less vascularity, providing a firmer tumor to handle, and with less extrarenal extension. There are arguments for and
against the SIOP versus the COG initial therapies, however the COG Renal Tumors Committee feels that staging (i.e. lymph node status) and pathological data is critical to accurate determination of appropriate risk-based therapy. Therefore, prenephrectomy chemotherapy is not routinely recommended in COG therapeutic studies for unilateral Wilms' tumor.

In conclusion, surgeons must exercise caution when attempting to primarily resect right-sided and/or large (≥12 cm) renal tumors as each factor is associated with an increased risk for IOS.

In a case reported from Singapore, peritoneal metastases resulted from laparoscopic partial nephrectomy performed for localized WT after 3 months from the primary surgery. (Chui CH, Lee AC 2010)

Chylous Ascites

Chylous ascites after nephrectomy for WT had been reported by Weiser AC et al. where extensive lymphadenectomy was associated with this complication. However, the practice of Lymph node sampling and not extensive lymph node dissection, in addition to meticulous lymphostasis, significantly decreased this complication. Management was done successfully through conservative treatment in most cases. Few cases required abdominal exploration. (Weiser AC et al, 2003)
RECURRENT DISEASE

Recurrent disease is difficult to treat in children with WTs. Most recurrences happen by 18 months. The tumor bed and the lungs are the 2 most frequent sites of recurrence. There were 2 research strategies that were tested on NWTS-5: stratum for those with stage I and stage II disease and stratum C for those who had relapse after radiotherapy. The role of surgery in recurrent disease is still undefined. In most cases, if there is residual disease after initial surgery that can be removed and result in a gross cure, surgery should be considered. *(Kieran K et al, 2015)*

The most common sites of WT recurrence are the lungs, liver, opposite kidney, and intraabdominal sites, including the original tumor bed. WT occasionally recurs in the brain, bone, and distant lymph nodes. Most relapses are diagnosed within the first 2 years after the original diagnosis.

**Factors associated with favorable prognosis after recurrence** include favorable histological features, initial treatment with only vincristine and actinomycin D, recurrent disease involving the lungs only, recurrent disease arising in the abdomen of a patient who did not receive abdominal irradiation, and relapse more than 12 months after the original diagnosis. With aggressive therapy, approximately 60% to 80% of patients with tumors with favorable prognostic features can be cured. *(Dome JS et al. 2002)*
PROGNOSIS

Despite some adverse risk factors that decrease prognosis (metastases, unfavorable histology, recurrent disease, and loss of heterozygosity of both 1p and 16q), most children with Wilms' tumor have a very favorable prognosis. Overall the survival of children with Wilms' tumor approaches 90%, with some risk factors (low stage, favorable histology, young age, low tumor weight) conferring even better outcomes. Thus, Wilms' tumor is at the top of the list for best outcome of the common pediatric solid tumors.

Multiple studies had evaluated the factors that predict WT relapse. A Japanese study performed by Aoba T et al evaluated 33 cases of FH-WT who had undergone upfront nephrectomy. They concluded that the histological subtype pre-treatment BPT-WT (blastemal predominant type WT) should be included as a strong indicator of poor prognosis and such patients should be treated as a high-risk group (Aoba T et al 2012).

Other Prognostic Factors

As the treatment regimens for children with Wilms' tumor have become more effective, the ability of retrospectively determined prognostic factors to predict outcomes is diminished. Traditional staging factors, such as tumor size, histology, and lymph node metastases, relied upon in the past to predict risk for tumor progression or relapse, are now less able to stratify FH patients for treatment. Clinical cancer trials are now evaluating biologic factors that may predict tumor behavior.

Loss of heterozygosity: LOH for a portion of chromosome 16q and/or 1p has been noted in 20% of Wilms' tumors. This is associated with an increased risk for relapse (Grundy et al, 1994, 2005; Wittman et al, 2007). This difference in outcome is independent of histology and stage. NWTS-5
patients with stage I-II FH tumors with LOH of either 1p or 16q had an increased risk of relapse and death in comparison with patients lacking LOH at either locus (Grundy et al, 2005). The risks of relapse and death for patients with stage III to IV FH tumors were increased only with LOH for both regions. These results have been incorporated into the current COG renal tumor protocols. Children whose tumors demonstrate LOH for these chromosomal regions will receive an intensification of treatment.

Another potential marker is telomerase, a reverse transcriptase that maintains chromosome ends, compensating for the loss of DNA that occurs in replication. High telomerase activity has been found to be an unfavorable prognostic feature for several types of cancers. A case cohort study involving 291 patients confirmed the correlation between telomerase RNA expression and recurrence, and this was independent of tumor stage in multivariate analysis (Dome et al, 2005). Future studies will seek to evaluate how telomerase expression may be used in conjunction with other prognostic markers, such as LOH at 1p and 16q, to stratify patients into risk-appropriate treatment groups.

**DNA Content:** The proliferative rate of tumor cells can be estimated by the measurement of DNA content. Aneuploidy occurs more frequently in anaplastic histology tumors, but findings in FH tumors are inconclusive. The correlation between cellular DNA content and prognosis was examined in the NWTS-5 cohort. A DNA index greater than 1.5 was strongly associated with anaplastic histology and predictive of poor outcome. However, DNA content was not predictive of outcome when stratified by histology and stage (Ehrlich, 2007).

**Cytokines:** The growth of solid tumors is critically dependent on the induction of neovascularity by angiogenic cytokines. Vascular endothelial growth factor (VEGF) is an angiogenic cytokine detected with increased
frequency and quantity in experimental and clinical specimens of Wilms’ tumor (Kayton et al, 1999; Karth et al, 2000). In experimental animals, lung metastases were far more likely to occur in animals with VEGF positive tumors. Anti-VEGF therapy has been shown to suppress tumor growth in mice and can prevent development of metastases (Rowe et al, 2000; Frischer et al, 2004). Antiangiogenesis treatment would appear to be a promising adjunctive future treatment for patients with Wilms' tumor.
PATIENTS
AND
METHODS
PATIENTS and METHODS

This is a prospective cohort study involving children with unilateral renal masses, diagnosed as unilateral WT based on clinical and radiological data, presenting to the Children Cancer Hospital of Egypt (CCHE) in the period between January 1st 2009 and January 1st 2012. All tumor stages (I-IV) were enrolled in the study excluding bilateral cases (stage V).

The following cases were also excluded (see table 4) based on the current COG protocol for treatment of unilateral WT.

(Table 4) Exclusion criteria of the study based on COG protocol

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologically evident massive extrarenal extension.</td>
<td>These cases will inevitably receive radiation therapy.</td>
</tr>
<tr>
<td>Radiologically evident bulky paraaortic lymph nodes.</td>
<td></td>
</tr>
<tr>
<td>Cases with suprahepatic/retrohepatic IVC malignant thrombi.</td>
<td>The setup of ultra-major surgery with the need of cardiopulmonary by-pass isn’t available.</td>
</tr>
<tr>
<td>Extensive pulmonary deposits making the child unfit for general anaesthesia</td>
<td>Preoperative chemotherapy is indicated</td>
</tr>
<tr>
<td>Solitary kidney</td>
<td></td>
</tr>
<tr>
<td>Horseshoe kidney if upfront surgery is not feasible</td>
<td></td>
</tr>
</tbody>
</table>

Upfront nephrectomy decision for every single case was taken during the multidisciplinary meeting. Informed consent was obtained from the parents of every child. Radical nephrectomy and lymph node sampling (hilar & paraaortic areas) was the standard procedure.

After surgery, pathologic confirmation of WT was carried out in all cases. The patients then were classified according to the histology (either favorable or unfavorable histology) and stage into three groups: low, intermediate and high risk groups. We used the staging system as depicted by the
Further treatment (chemotherapy/radiotherapy) was tailored according to the risk category. Cases proved to be non WT histopathologies were excluded. See figures (12,13,14,15)

We identified a retrospective cohort as a control group including cases that were diagnosed as unilateral WT and received preoperative chemotherapy (PC group) based on the SIOP protocol before January 1st 2009. We excluded 2 cases - that were initially locally advanced on imaging - from the comparison to overcome selection bias that may be present in the principal study group (UN group) and to render both groups similar as regard stage distribution. Treatment protocols are shown in the next figures.(12,13,14)

![Figure 12: Treatment algorithm of WT adopted in Children Cancer Hospital](image1.png)

![Figure 13: Stage adjusted treatment of WT adopted in CCHE for FAVORABLE HISTOLOGY WT. EE-4A: vincristine and dactinomycin, for a period of about 19 weeks. DD-4A: vincristine, doxorubicin and dactinomycin for a period of about 25 weeks.](image2.png)
Radiation therapy is given to all patients. **Regimen M**: vincristine, dactinomycin, and doxorubicin alternating with four cycles of cyclophosphamide/etoposide and radiotherapy

**Figure 14**: Stage-tailored surgical responsibilities.

**Figure 15**: Stage adjusted treatment of WT adopted in CCHE for **UNFAVORABLE HISTOLOGY WT**. DD-4A–HR: vincristine, doxorubicin and dactinomycin for a period of about 25 weeks. Radiation therapy is given to all patients. **Regimen UH - HR**: vincristine, dactinomycin, and doxorubicin alternating with four cycles of cyclophosphamide/etoposide and radiotherapy

Charts of all patients were reviewed. Collected data included:

- Demographic variables; age at time of diagnosis (months), sex, cases of WT associated with familial syndromes.
- Details of clinical variables: laterality, histopathologic variables, preoperative and postoperative stages.
- Surgical variables: Incision, intraoperative planned and unplanned steps, intraoperative complications, as well as early and delayed postoperative complications.
- Event free survival and overall survival data.

Follow up of all cases was done in the same institution (i.e CCHE). The minimal follow up period was **30 months**. Events include: local or distant recurrences. End points include: the end of the study (July 1\textsuperscript{st} 2014) or death of the patient.
Data was analyzed using SPSSwin statistical package version 16. Numerical data will be expressed as mean ± standard deviation, median and range as appropriate. Qualitative data will be expressed as frequency and percentage. Chi-square test (Fisher’s exact test) will be used to compare two studied groups regarding qualitative variables. For quantitative data, comparison between two groups will be done using either parametric or non-parametric t-test as appropriate. Survival analysis will be done using Kaplan-Meier method. Comparison between two survival curves will be done using Log-rank test and p-value ≤ 0.05 will be considered significant.
RESULTS
RESULTS

- Among the 153 children presented with unilateral renal masses, diagnosed as Wilms’ tumor (WT), based on clinical and radiological data, and registered at the CCHE outpatient clinic during the study period, 72 cases were eligible to be enrolled in our study to receive upfront nephrectomy (UN) according to the COG protocol.
- The other 81 cases were excluded from our study as shown before and were planned for preoperative chemotherapy (PC) according to the exclusion criteria of COG protocol as shown in table (5). Two reasons were behind the exclusion of this group from our comparative study, though comprising more patients than the principal study group: first, most of its cases are stage III 74/81 (91%), something that made this group non equivalent to the UN group that has all stages within its population. Second, the principal aim of the study is to compare the surgical outcome of upfront surgery compared to delayed surgery, but not comparing the whole protocols i.e. (COG Vs SIOP)

(Table 5) Excluded cases from enrollment into the study

<table>
<thead>
<tr>
<th>Cause of exclusion</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologically evident massive extrarenal</td>
<td>33</td>
</tr>
<tr>
<td>extrarenal (extracapsular) extension.</td>
<td></td>
</tr>
<tr>
<td>Radiologically evident bulky paraaortic lymph nodes</td>
<td>18</td>
</tr>
<tr>
<td>Supra/retrohepatic IVC thrombus</td>
<td>11</td>
</tr>
<tr>
<td>Previous true cut biopsy</td>
<td>12</td>
</tr>
<tr>
<td>Extensive lung deposits</td>
<td>5</td>
</tr>
<tr>
<td>Extensive hepatic deposits</td>
<td>1</td>
</tr>
<tr>
<td>Horseshoe kidney</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>81</strong></td>
</tr>
</tbody>
</table>
A retrospective cohort including all patients of WT who were managed by preoperative chemotherapy (PC) before January 2009 (n=35) was considered for comparison (control group) after exclusion of radiologically identified locally advanced cases as explained in the previous section, to make it more or less similar -regarding stage distribution- to the principal study group.

In this section, for each studied variable(s), I will provide the results of the whole study population as an indicator of the institutional experience, followed by a comparison between the two study cohorts i.e the prospective Upfront Nephrectomy (UN) cohort and the retrospective Preoperative Chemotherapy (PC) cohort. See next table (6).

(Table 6) Summarized comparison between the study cohorts

<table>
<thead>
<tr>
<th></th>
<th>Upfront nephrectomy (UN) group</th>
<th>Preoperative chemotherapy (PC) group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment protocol</td>
<td>COG protocol</td>
<td>SIOP protocol</td>
</tr>
<tr>
<td>Total number of cases</td>
<td>72</td>
<td>35</td>
</tr>
<tr>
<td>Mean age</td>
<td>28.46 months, SD 19.86</td>
<td>39.57 months, SD 28.36</td>
</tr>
<tr>
<td>Stage distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stage I</td>
<td>41 (57%)</td>
<td>11 (31.4%)</td>
</tr>
<tr>
<td>stage II</td>
<td>18 (25%)</td>
<td>9 (25.7%)</td>
</tr>
<tr>
<td>stage III</td>
<td>9 (12.5%)</td>
<td>8 (22.8%)</td>
</tr>
<tr>
<td>stage IV</td>
<td>4 (5.5%)</td>
<td>7 (20.1%)</td>
</tr>
<tr>
<td>Resectability</td>
<td>67 (95.3%)</td>
<td>35 (100%)</td>
</tr>
<tr>
<td>Lymph node harvest</td>
<td>Mean (6.2 lymph nodes)</td>
<td>Mean (5 lymph nodes)</td>
</tr>
<tr>
<td>Favorable histology WT</td>
<td>64 (88.8%)</td>
<td>31 (88.5%)</td>
</tr>
<tr>
<td>Perioperative (intra and post operative) complications</td>
<td>9/72 (12.5%)</td>
<td>11/35 (31.4%)</td>
</tr>
<tr>
<td>Three years event free survival (EFS)</td>
<td>87.3%</td>
<td>76.8%</td>
</tr>
<tr>
<td>Three years overall survival (OS)</td>
<td>95.8%</td>
<td>79.6%</td>
</tr>
</tbody>
</table>
The whole study population \( n = 107 \) included 54 males, 53 females. The mean age at diagnosis was 32.215 months. Sixty-one cases were less than 2 years in age (57%), of whom 2 cases was diagnosed at birth. Maximum age at diagnosis was 7 years. The age distribution within the different stages is shown in the next boxplot (Figure 15).

Figure 16: This boxplot shows that children with older ages are more among later stages. Two cases in the whole study population were diagnosed at birth.

The mean age (months) at diagnosis of children in the UN (upfront nephrectomy) group was younger than that of the preoperative chemotherapy (PC) group (28.46 months, SD 19.86) Vs (39.57 months, SD 28.36) respectively.

Figure 17: This boxplot shows age distribution among the 2 arms, note that children in UN group are younger than PC group.
The most common presentation was **painless abdominal mass** \( n=81 \). Other presentations are shown in table (7). Preoperative hypertension was reported in 12 cases. Only 5 cases were associated with clinical syndromes, i.e. familial cases. **Forty-three** cases occurred on the right side (40.2%), whereas left sided tumors counted 64 (59.8%).

(Table 7) Different presentations of WT

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Swelling</td>
<td>81</td>
</tr>
<tr>
<td>Hematuria</td>
<td>10</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>2</td>
</tr>
<tr>
<td>Testicular swelling</td>
<td>2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>107</strong></td>
</tr>
</tbody>
</table>

**Stage distribution** at presentation (table 8) showed that most cases are stage I.

(Table 8) Stage distribution of the whole study population

<table>
<thead>
<tr>
<th>Stage</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>54</td>
</tr>
<tr>
<td>Stage II</td>
<td>23</td>
</tr>
<tr>
<td>Stage III</td>
<td>19</td>
</tr>
<tr>
<td>Stage IV</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>107</strong></td>
</tr>
</tbody>
</table>

**Eleven** cases were assigned **different stages** at the final histopathological assessment as compared to the initial staging that was based on clinical & radiological grounds. Ten of them were in the **PC** group (28.5%), where 5 cases were upstaged and the other 5 are downstaged. Among the **UN** group, only one case was upstaged. (1.3%).
• Of the 11 cases presenting as stage IV, 4 of them (pulmonary metastases) were in the UN group and they were subjected to UN in this setting as stated by the study protocol. The other 7 cases (pulmonary/4 – hepatic/3) were in the group of PC.

• Differential stage distribution between the two proposed groups was the following:
  UN group: stage I 41(57%), stage II 18(25%), stage III 9(12.5%), stage IV 4(5%). For the PC group, postoperative staging was made according to the SIOP protocol with the following distribution: stage I 11 (31.4%), stage II 9(25.7%), stage III 8(22.8%), stage IV 7(20%).

Upon surgical exploration, five cases that were planned for upfront surgery were found to be irresectable though the decision of the attending surgeons was upfront surgery. Those cases were referred for chemotherapy and delayed surgery. The rest of cases either in the UN group (n=67) or the PC group (n=35) were successfully resected by radical nephrectomy. All cases within both groups were subjected to radical nephrectomy.
In only two cases of the whole population study, tumor was found at the resection margins upon histopathological assessment, so, resection margins were free of tumor in 105 cases (98%).

- **Lymph node sampling** was successful in 97 cases (90.6%), while in the remaining 10 cases no lymph nodes were retrieved from the specimen. The minimal number of sampled lymph nodes was 1, while the maximal was 25. The mean number of lymph node sampled was 7 lymph nodes. The mean total number of harvested lymph nodes among the UN group was 6.2 lymph nodes, while that of the PC group was 5 lymph nodes.

- Tumor extends to the adrenal gland in only 5 cases (4.6%) in the whole study population. It was free of disease in 100 cases, with the remaining 2 cases with missing data about the adrenal gland involvement. **Adrenal sparing nephrectomy** was successfully performed in 43 cases of the total study population. They were 27 cases (37.5%) and 16 cases (45.7%) among the UN and PC groups respectively.

- **Renal vein malignant thrombus** was encountered in 9 cases in during post operative histopathological assessment, 6 of them within the UN group and the rest were within the PC group.

- Infra hepatic IVC malignant thrombus was found in 3 cases in the whole study population, one of them was encountered in the UN group. IVC Thrombectomy was successfully accomplished in all 3 cases.

- Favorable histology WT (FH-WT) without anaplasia was found upon histopathological assessment of 95 cases (88.8%), whereas unfavorable histology was found in the rest of cases (12), 8 of them presented diffuse anaplasia (6.5%) and 4 cases presented focal anaplasia (3.7%). The FH-WT cases among the study cohorts were 64 in the UN group (88.8%) and 31 in the PC group (88.5%).
The risk score for the study population revealed that intermediate risk cases were 78 (72.9%), 6 cases have low risk (5.6%) and high risk cases counted 23 (21.5%).

Unplanned operative steps were taken during only 4 nephrectomies (3.7%). These include: non anatomic hepatic resection, excision of part of diaphragm, excision of part of Psoas muscle (i.e posterior abdominal wall) and splenectomy was done for one case due to inadvertent splenic vascular injury.

The overall rate of intraoperative complications was 5.6% (6/107). They included the following: intraoperative rupture (2), diaphragmatic/pleural injury (2) and Massive hemorrhage that needed intraoperative and post-operative blood transfusion (1).

Intraoperative tumor rupture/spill with subsequent spillage occurred in two cases only in the whole study population. In one case, there was massive soilage. In the other one, only focal disruption of the tumor capsule occurred with minimal soilage.

The overall rate of postoperative complications was 11% (12/107). The most common early post operative complications (i.e within 30 days) was intestinal obstruction that was seen in 3 children, their diagnoses were ileocecal intussusception (2 cases) and adhesive IO (1case). Laparotomy and reduction was done for intussusception without the need of intestinal resection. Release of adhesion was just needed for adhesive IO.

Other early post operative complications include: lymphorrhea (2 cases) and aspiration pneumonitis (1 case).

Also, the commonest delayed (beyond 30 days) post operative complication was intestinal obstruction (6 cases). The cause in all cases was adhesions. All 6 cases required admission and surgical exploration. Adhesiolysis was
required in 4 cases. The remaining two needed intestinal resection and anastomosis.

- The incidence of perioperative (intra and post operative) complications in the both groups was different. In the UN group it is 9.7% (7/72), whilst for the PC group it was 31.4% (11/35).
- The incidence of intestinal obstruction was equal among both groups (6 cases each). Noteworthy that intestinal obstruction was mostly an early complication within UN group (5/6), whilst it was absolutely a delayed complication in the PC group (6/6).

- **Locoregional recurrence** occurred in 7 cases of the study population (6.5%), in one case the recurrence occurred in the paraaortic area, the other 6 all recurred in the operative bed. The time interval between surgery and local recurrence ranges between 7 & 37 months, mean interval is 20 months. Complete resection with safety margin for the recurrent cases was the rule, but in the case of paraaortic nodal recurrence, resection was incomplete. Incidence of local recurrence among the UN group was 3/72 (4.2%). In the PC group it was 4/35 (11.4%).

(Table 9) Summary of surgical events for the whole study population

<table>
<thead>
<tr>
<th>Number</th>
<th>Unplanned operative steps</th>
<th>4/107 (3.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intraoperative complications</td>
<td>5/107 (4.7%)</td>
</tr>
<tr>
<td></td>
<td>intraoperative rupture (2), diaphragmatic /pleural injury (2) and Massive hemorrhage (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early (within 30 days) post operative complications</td>
<td>7/107 (6.5%)</td>
</tr>
<tr>
<td></td>
<td>Intestinal obstruction (3), lymphorrhea (2) and aspiration pneumonitis (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delayed (beyond 30 days) post operative complications</td>
<td>8/107 (7.5%)</td>
</tr>
<tr>
<td></td>
<td>Intestinal obstruction (6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Locoregional recurrence</td>
<td>7/107 (6.5%)</td>
</tr>
<tr>
<td></td>
<td>Operative bed (8), paraaortic nodes (1)</td>
<td></td>
</tr>
</tbody>
</table>
At the end of the study (July 2014), the least follow up period was 30 months and the longest was 59 months. Only 3 patients were lost to follow up. Among the UN group, 67 patients were alive (93%). Twenty seven patients were alive among the PC group (77%).

The mean event free survival (EFS) duration for the whole study population was 40 months. The 3 years EFS rate of the UN group was 87.3% as compared to that of the PC group which was 76.8%. However, this difference wasn’t statistically significant [Log Rank (Mantel-Cox) test estimated P-value was 0.27]. (figure 17,18)

Figures 18, 19: Showing EFS and OS for the study population.
The mean overall survival (OS) duration was **42.8 months** for the whole population. There was a statistically significant difference when comparing the 3 years overall survival (OS) rate between the two study cohorts, which was **95.8%** in the UN group and **79.6%** in the PC group. [Log Rank (Mantel-Cox) test estimated P-value 0.003].

**Figure 20, 21**: Survival curves showing EFS & OS for both groups in the study.
DISCUSSION
DISCUSSION

From the opinion of many cancer care professionals, including surgeons, pediatric oncologists, radiotherapists, as well as medical statisticians; treatment of Wilms' tumor (WT) is a story of success along the past decades. The management of this pediatric malignancy dates back to the middle of 19th century, with evolving of treatment modalities and approaches in the years thereafter.

Two schools of management of WT are leading the clinical trials as well as the treatment approaches: The SIOP approach (according to International Society of Pediatric Oncology) or the European school and the COG approach (according to Children Oncology Group, formerly known as the NWTSG) in North America and Canada.

The adoption of the preoperative chemotherapy is the landmark of the (SIOP) approach, while upfront nephrectomy is the primary treatment modality pursued by the (COG).

Although this debate, the current evidence is that most patients with Wilms’ tumor survive long term, regardless of the sequence of therapeutic interventions. Modern treatment regimens yield overall survival rates of 90%, and this success has precipitated a shift in emphasis to reducing toxicity and complications of different treatment modalities.

By the year of 2009, the COG approach became the adopted treatment pathway in the most prominent children cancer treatment and research center in Egypt, namely the Childen Cancer Hospital in Egypt (CCHE) that had been launched in 2007.

- The purpose of this study was to evaluate the outcome of children with unilateral WT treated with upfront nephrectomy (UN) based on the COG
protocol and to compare it with those treated with preoperative chemotherapy (PC) based on the SIOP approach. A detailed assessment of the surgical outcome regarding local recurrence and perioperative complications was also performed.

- Also, we introduce the experience of our institution in the treatment of WT, with the impact of local demographic, clinical and socioeconomic characteristics. That’s because by the end of the enrollement period and even in the years thereafter, the flow of WT patients to the hospital showed significant case load. So, our institutional experience - being the first specialized children cancer center in the Middle East and Africa - is a potential source of high level evidence regarding treatment of pediatric malignancies.

- Another goal is to assess the feasibility and safety of the UN in a unique set up; that’s a specialized center in a developing country. An issue that was raised in some reports arguing against the adoption of upfront surgery in a developing country.

- The third United Kingdom Children’s Cancer Study Group (UKCCSG) Wilms’ tumour trial (UKW3) was the only prospective randomized trial that compared two arms representing the two treatment pathways i.e upfront surgery Vs preoperative chemotherapy. This study extends between 1991 and 2001 and a total of 186 cases were enrolled in its two arms. It is a landmark study addressing the longlasting debate of treatment of WT. (Mitchell et al. 2006)

- During our study period (3 years), 153 children with WT presented to the outpatient clinic for medical care. When looking at the number of cases presenting to our center, one can identify the steady increment of the case load. The case load is about 50 case/year which is much more than reported
series in other trials including the UKW3, giving more areas of research regarding all characteristics and treatment approaches of this disease.

Also, the case load in our series highlights the fact that a center of excellence in a developing country – and not dispersed efforts - is an ideal situation and soon becomes a drainage center, something that has its impact on the clinical experience and learning curve of medical personnel therein. That’s of course, in addition to improving the clinical outcome of patients based on high level of evidence from large study population.

**Another major difference** in favour of our study is the application of upfront surgery for stage IV cases, which is a unique feature of the COG protocol and hence our series. Though the number of such cases (n=4) was not high in the study period (Jan 2009- Jan 2012), those cases were more in subsequent years.

**In our study**, since enrollment of cases that is eligible for UN had excluded a significant number of cases (n=81). It is noticed that more cases were excluded than enrolled into UN group. It is crucial to evaluate these cases from a surgical standpoint to evaluate their outcome, since they may be overtreated due to selection bias.

- Regarding the **epidemiological variables** reported in international series, approximately 400 new cases are seen every year in the United States. Close to 50% of tumors arise in patients who are younger than 3 years and 90% arise in patients who are younger than 6 years with a median age of 3.5 years. Nephroblastoma is significantly less common in the neonatal period, adolescence, and adulthood. There is no significant sex predilection. 

**In our series;** the annual incidence is largely an indicator of the whole country since the center is becoming a drainage destination for WT cases from nearly all pediatric health care levels throughout the whole country starting from July 2007. The annual incidence as reported above is about 50
cases/year. The median age in our study was **2.6 years**. Fifty-seven % of cases were less than 2 years, 88% were less than 6 years. The younger age of the UN group (**2.3 Ys**) as compared to that of the PC group (**3.3 Ys**) may be due to increased public awareness towards the cancer disease in the pediatric group in general, so, more cases come at early time within the course of their disease. Males and females were equally affected.

- **Stage distribution** within the UKW3 study showed less advanced stages within the PC group as compared to the UN group; **stage I**: 65.2% versus 54.3%; **stage II**: 23.9% versus 14.9%; **stage III**: 9.8% versus 29.8%, \((v^2\text{ test for trend } = 7.02, p = 0.008)\). \((\text{Mitchell et al. 2006})\). However, this difference is argued against most of the time as being an impact of chemotherapy and not a true different stage distribution. In addition, one of the prominent drawbacks of the PC approach is the loss of staging criteria with subsequent potential inaccurate stage assignment and suboptimal adjuvant treatment.

**In our series, distribution** showed that most cases are stage I: 54 cases (50.5%). Stage II cases were 23 \((n=21.5\%)\), stage III 19 (17.8%). Stage IV cases counted 11 i.e (10.3%). **Stage for stage comparison between both study groups** showed that UN group has less percent incidence of advanced stages. Again, what’s unique in our study is the inclusion of stage IV cases.

- Data from **National WT Study (NWTS) 4-5** showed that lymph node sampling/documentation during surgery was accomplished in 99% of cases. More important conclusion was that the likelihood of finding a positive lymph node and hence proper staging was greater when **more than 7 LNs** were sampled. \((\text{Kieran et al. 2012})\). The UKW3 study \((\text{Mitchell et al. 2006})\) had no comments about the numbers and impact of lymph node sampling.
In another large series entailing the issue of lymph node sampling and its impact, Zhuge et al. reported successful sampling/documentation in 74% of cases. They concluded that failure to biopsy lymph nodes for WT patients not only increases the risk of local recurrence due to understaging and inadequate adjuvant therapy, but is also an independent prognostic indicator of lower survival. (Zhuge et al. 2011)

In our series, lymph node sampling/documentation was accomplished in 90.6% of cases. A mean of 7 lymph nodes was harvested for the whole study population. Thus, it is consistent with the consensus about the proper number of lymph nodes needed for accurate treatment planning. (Kieran & Ehrlich 2015). The lymph node harvest for the UN group in our series was more than that of the PC group which has a better impact on stage determination and hence tailoring the appropriate treatment. Also, this reflects better learning curve.

A review of nephrectomy for nonmetastatic disease in NWTS-4 and NWTS-5 found adrenal involvement in 4.4% of patients, but similar overall and event-free survival (EFS) in patients who had undergone adrenalectomy or adrenal preservation. There were no cases of adrenal insufficiency in any child with a unilateral WT. (Moore K et al. 2010) (Kieran K et al. 2013).

In our series, adrenal gland was histologically involved by the tumor in 4.6% of cases. Meanwhile, adrenal sparing was done in 40% of surgeries only. So, the practice of adrenal preserving radical nephrectomy should be pursued in every case, so long as there is no absolute evidence of invasion.

The current recommendation is that the adrenal gland should remain in situ if possible, but not at the risk of rupturing the tumor. (Kieran K et al. 2015)
Surgical problems may affect outcome by delaying the start of postoperative therapy. In the **NWTS-3** study, a **19.8%** surgical complication rate was reported. A random sample of 534 patients treated on the **NWTS-4** was selected for in-depth review of surgical complications. Seventy-six complications occurred in 68 **12.7%** of the 534 children compared with 19.8% in NWTS-3 (P < 0.001), including bowel obstruction (5.1%), wound infection (1.9%), vascular injury (1.5%), splenic injury (1.1%), and diaphragmatic tear (0.4%). One patient (0.2%) each had liver injury, chylous ascites, incisional hernia, pulmonary embolus, respiratory failure, pleural effusion, pneumothorax, urinary tract infection, pancreatitis, and staphylococcal sepsis. (*Ritchey et al. 2001*)

- In his series, **Stehr M et al** reported overall rate of intraoperative complications to be **18%**. He noticed higher rate for the UN group (**25%**) as compared to PC group (**8%**). Specifically, he reported increased rate of intraoperative spill for the children treated with UN: while only one case of PC group had intraoperative tumor rupture. (*Stehr M et al 2004*)

- Intraoperative tumor spill rate has been reported to be less after preoperative therapy with a rate of **6%** in the **SIOP-5** study compared with **20%** in **NWTS-4**. However, SIOP reported only gross spill whereas NWTS included local spills.

- **In Hall’s series**, the rate of tumor rupture at surgery after PC was very similar to the SIOP rate at 5.3%, but the spill rate with primary surgery—2 (4.3%) of 46 patients—was lower than that quoted by the NWTSG. (*Hall et al. 2006*)

- **The overall rate of perioperative complications in our series** was 20/107 (**18.7%**). As shown above, it is similar to other international series. Also, we had cases of intestinal obstruction as the commonest complication
like other international reports. The difference in timing of this complication to be early within the UN group and late within the PC group raises some concerns and needs in-depth assessment and addresses the need for modification in surgical technique so as to decrease the incidence of this complication. There is an already ongoing study that addresses this issue in CCHE.

Intraoperative rupture/spill occurred only twice in our whole study population, both cases were among the UN group i.e 2/72 (2.7%) which is similar to recent series. Following a stepwise approach while operating on huge mass in a child is crucial to avoid this complication, starting from the operative incision till freeing the mass from surrounding fascial layers and vascular control.

Also, we hadn’t any incidence of Chylous ascites that had been reported in other series. The use of state-of-the-art sealing devices in addition to proper lymphostasis are important intraoperative tools that may prevent this complication.

- In NWTS-4, the relapse-free survival was 85.9% in the group with no spill and 76.5% if a local spill was reported; the overall survival at 8 years was 94.2% and 91.9%, respectively. (Shamberger et al. 1999)

- In the series done by Hall G et al., which comprises two cohorts representing UN and PC treatment pathways, despite the treatment reduction in the delayed surgery arm, there was no statistically significant difference in outcome between the two treatment approaches with respect to event-free or overall survival. (Hall et al. 2006).

- Also, in the UKW3 study, Mitchell et al. noted similar event free survival and overall survival regardless of the treatment approach. (Mitchell et al. 2006)

- Our series shows a statistically significant better overall survival for the UN group. The event free survival was in favor of the UN cohort, but
the results were not statistically significant. This difference in the overall survival may be the result of multiple factors other than true survival factors; more advanced cases in the PC group and selection bias. The selection process for enrollement of cases into the study underscores a debatable issue in the eligibility criteria of the COG, which is the subjective view of the operating surgeon, a condition that may deprive other cases of radiologically apparent stage III from a same chance of upfront surgery.

**Our study** was done to determine also that UN doesn’t result in increased surgical morbidity and mortality. Also, it has been assumed that the approach of PC is more suitable for developing country, and the results of our study addressed this issue. The practice of UN in high volume center is a safe and feasible treatment pathway.

- In his retrospective series, Stehr et al reported 8 cases out of 39 treated with preoperative chemotherapy to be non WT on final pathological examination. *(Stehr M et al 2004). In this series*, only one case in the PC group was diagnosed after surgery as renal cell carcinoma.

- One of the advantages of the PC approach is that its administration is considered in vivo testing of the tumor response, a condition that enhances a tailored post operative treatment.

- A **downside** of the UN approach is that minimally invasive surgery (MIS) is not feasible, since a preoperative chemotherapy is mandatory for this approach. In both the UKW-3 study and Stehr's study, MIS was not performed for either study arms. *(Mitchell et al. 2006) (Stehr M et al 2004). In some reports, upfront laparoscopic nephrectomy was performed in highly selected cases. *(Barber et al. 2009) (Javid et al. 2011).*
In our series, all cases underwent conventional open surgery. The adoption of laparoscopic nephrectomy for WT is an area ongoing research that necessitates preset selection criteria.

- Another drawback of the UN approach is the inability to perform partial nephrectomy (or nephron sparing surgery) most of the time. This factor has emerged lately due to the recent data demonstrating that renal preserving surgery decreases the likelihood of chronic renal disease and associated co-morbidities. Although the improved imaging, anesthesia and surgical techniques have prompted some surgeons to consider nephron sparing surgery (NSS) in children with unilateral WT, this is a highly controversial topic. (Kieran K et al. 2015).

Cost NG et al. have addressed this issue by analyzing oncologic outcomes of patients after partial nephrectomy (PN) for unilateral WT. They identified all published cases (n=82) of PN for unilateral WT and compared their outcome with that a cohort of radical nephrectomy at their institution. After controlling for stage, there were no statistically significant differences in the oncologic outcomes between the two groups. They concluded that PN for appropriately selected patients with UWT should be studied in prospective, co-operative group trials. (Cost NG et al. 2011)

However, those who are arguing against the adoption of NSS for unilateral WT refers to a report from the SIOP 2001 protocol. In this study, although not formally recommended, upfront chemotherapy was administered for 4 weeks followed by nephron sparing surgery. Successful NSS was performed in only 3% of patients, and negative margins were achieved in only one-third of patients. More importantly, in the stage III group, 58% had stage III disease because of positive margins. These patients received extrachemotherapy and radiotherapy that they would not have had if a nephrectomy were performed. EFS was slightly higher in this group, but
short-term overall survival was equivalent to that of those undergoing complete nephrectomy. (Zani A et al. 2005)

Ferrer et al. looked at the feasibility of performing partial nephrectomy in children in the ARENO532 very-low-risk study, and similar to the SIOP data, they found that only 9% of these children would have met the criteria. (Ferrar FA et al. 2013)

The most common reason that tumors were not considered amenable to NSS was location of the tumor relative to vascular structures; as NSS is typically performed after upfront chemotherapy, the proportion of children eligible for NSS may increase if neoadjuvant therapy were administered, but the risks of additional chemotherapy in this population must be considered, particularly in light of the already-excellent clinical results achieved using current surgical techniques. (Kieran & Ehrlich 2015)

There are several things to consider when interpreting reports. First, these all reflect a highly selected group of patients without standing expected EFS and overall survival. Second, WT start from nephrogenic rests and are often multifocal in nature. Therefore, one could be leaving behind premalignant cells that could clonally expand overtime. Third, although 5-year survival rates are equivocal, it is unclear that this is the optimal outcome standard. Consideration of performing NSS in a child with unilateral WT should be carefully thought out and possibly only performed in conjunction with a clinical trial. In the recent COG ARENO3B2 study unilateral partial nephrectomy for children with 2 healthy kidneys is not endorsed. (Kieran & Ehrlich 2015)

- In our series, NSS was not performed at all in view of the above rationale.
The psychological aspect of the upfront surgery is more evident as parent’s comfort towards this approach, they considered getting the tumor out of their child is a more valid option. This was valid also in Hall’s series. (Hall et al. 2006)

FINALLY, In depth analysis in another study is highly needed for the excluded cohort from our study. In addition to the significant number (n=81), this cohort comprises most of the locally advanced cases encountered at our center. The study of this cohort will shape up the complete institutional experience of the treatment of WT.
CONCLUSIONS

- Significant improvement has been made in the treatment of children with Wilms' tumor. New protocols are in place designed to maintain a high rate of cure for these patients while minimizing toxicity, based on refinement of the risk stratification system. Surgeons play a critical role in the management of children with Wilms' tumor and it is imperative that they understand the directives of these new protocols and how the conduct of an operation can influence therapy and outcome for these patients.

- Prognostic factors for risk-adapted therapy include age, stage, tumor weight, and loss of heterozygosity at chromosomes 1p and 16q. Histology has a major role in risk stratification of WT.

- The procedure of UN is a safe and feasible surgery, even in radiologically evident huge masses. That's because the adopted protocol entails stepwise approach to achieve the most important goal of surgery; avoidance of intraoperative spillage.

- The event free survival and overall survival of the two treatment pathways are nearly similar over the past decades.

- The adoption of UN nephrectomy approach is feasible in developing countries though there had been an argument against this approach in previous series. But this is not absolute, there should be a proper set up, in the form of center of excellence with experienced oncologists (surgical, medical, radiation and statistician). The presence of such set up may even raise the awareness of the public to the extent of changing the common presentations of WT in developing countries from huge masses to lesser volumes with less advanced stages.

- On the other hand, in this era of minimally invasive surgery, the procedure of UN has a risk of intraoperative spillage (IOS) with resultant upstaging, the need to flank irradiation and the risk of local relapse. So, strict
selection criteria must be followed to identify patients who are eligible for this surgery. By and large, the adoption of preoperative chemotherapy can render more patients for minimally invasive nephrectomy.

- Also, one of the main drawbacks of UN is inability to perform nephron sparing surgery for many cases, with still no available preoperative scores to define which patients of unilateral WT can benefit from NSS. This issue is raised whenever there is a precious kidney in a more vulnerable patient, e.g. syndromic cases.

- One of the selection criteria to enroll a case of WT to receive UN is the viewpoint of his operating surgeon. This subjective, experience-dependent judgement should be unified by a preset score when the patient is first seen in the multidisciplinary meetings.

- Minimizing the perioperative surgical morbidities should be the most important goal in all studies addressing surgical treatment of WT, namely intestinal obstruction.
SUMMARY

Wilms' tumor (WT) or nephroblastoma is the most common primary malignant renal tumor in children. Histology and Stage are the most important prognostic indicators for WT. There are currently two staging systems available reflecting treatment differences; the Children Oncology Group (COG) Wilms' tumor staging system and the International society of pediatric oncology (SIOP) staging system. The COG reflects staging at primary surgery. Alternatively, the SIOP is performed after preoperative chemotherapy. Surgery maintains an important role in treatment, though the improved prognosis for this malignancy during the 20th century is attributed primarily to advances in chemotherapy. Transperitoneal radical nephrectomy is the standard operative procedure for unilateral WT.

The most common intraoperative complications are tumor rupture and bleeding. Post-operatively, the most common complication is small bowel obstruction occurring in more than 5% of patients. The Importance of multidisciplinary management teams in pediatric solid tumors is clearly evident in the cooperative groups’s trials that were constructed for Wilms’s tumor.

This prospective cohort study was conducted for children with unilateral renal masses diagnosed as WT, presenting to children’s cancer hospital from January 2009 to January 2012. Their treatment was based on the COG protocol. A retrospective cohort as a control group including cases that were diagnosed as unilateral WT and received preoperative chemotherapy based on the SIOP protocol before January 1st 2009. Charts of all patients were reviewed. The minimal follow up was [30] months.

We aimed at: assessment safety and feasibility of upfront surgery according to the COG protocol in view of our local demographic, clinicopathological and surgical variables, providing the institutional experience of treatment of
Wilms' tumor over 4 years duration in CCHE, comparing upfront nephrectomy (UN) for treatment of Wilms' tumor with radical nephrectomy after Preoperative Chemotherapy (PC) as regard the incidence and prevalence of perioperative complications and finally asessement the overall and disease free survival in both groups.

Initial investigations were, first to evaluate the primary tumor through physical examination, abdominal U/S with doppler and CT scan or MRI, second to exclude distant spread through CT chest. After surgery, the patients were classified according to the histology and stage into three groups: low, intermediate and high risk groups.

Among the 156 children presented with unilateral renal masses quiry of WT and registered at the CCHE outpatient clinic during the study period, 72 cases were eligible to be enrolled in our study to receive upfront nephrectomy (UN) according to the COG protocol. The retrospective cohort chosen for comparison counted 35 children. The whole study population (n = 107) included 54 males, 53 females. The mean age at diagnosis was 32.215 months. Age was slightly higher in the UN group than the PC group. The most common presentations was painless abdominal mass n=81.

Five cases that were planned for upfront surgery were found to be irresectable. Resection margins were free of tumor in 105 cases (98%).

**Lymph node sampling** was successful in 97 cases (90.6%).The mean number of lymph node sampled was 7 lymph nodes. **Lymph node harvest was better in the UN group.** Tumor extends to the adrenal gland in only 5 cases (4.6%).

**Unplanned operative steps** were taken during only 4 nephrectomies (3.7%). The overall rate of **intraoperative complications** was 5.6% (6/107). The overall rate of **postoperative complications** was 11%
The most common early post operative complications (i.e within 30 days) was intestinal obstruction. The commonest delayed (beyond 30 days) post operative complication was intestinal obstruction (6 cases). The cause in all cases was adhesions. All 6 cases required admission and surgical exploration. More complications occurred with the PC group. Locoregional recurrence occurred in 7 cases of the study population (6.5%). The mean event free survival (EFS) duration for the whole study population was 40 months while the mean overall survival (OS) duration was 42.8 months at the end of study period. The EFS was better but not statistically significant among the UN group. OS was higher and statistically significant.


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ورم ويلمز هو أكثر أنواع سرطان الكلى شيوعا عند الأطفال، ويظل العلاج الجراحي ذا أهمية بالغة في علاج ورم ويلمز رغم أن الفضل في تحسن التاريخ المرضي لهذا المرض يعود بالفضل إلى التطورات البالغة في أساليب وطرق العلاج الكيميائي التي طرأت في القرن الماضي.

وهناك طريقتين لعلاج هذا الورم طبقا لمدرستين علاجيتين، المدرسة الأوروبية وفيها يتم إعطاء المريض العلاج الكيميائي قبل إجراء الجراحة، والمدرسة الأمريكية ويتم فيه الجراحة أولًا. ورغم أن النتائج متقاربة إلى حد كبير، إلا أن المقارنة بين طريقتين العلاج لأوزالنت تثير جدلا إلى الآن في الأوساط العلمية المهتمة بسرطان الأطفال. وفي مستشفى سرطان الأطفال بمصر، يتم تطبيق المدرسة الأمريكية منذ عام 2002، وفيما يلي دراسة مقارنة بين هذا الخط من العلاج، والخط الآخر الذي كان سائدا قبل بداية عام 2009.

أجرت هذه الدراسة المستقبلية على مدى ثلاث سنوات في مستشفى سرطان الأطفال بالقاهرة تحت إشراف أساتذة المعهد القومي للأورام- جامعة القاهرة في الفترة من يناير 2009 وحتى يناير 2012 وقد تضمنت الدراسة 107 مريضا بورم ويلمز على ناحية واحدة فقط (كل واحد)، حيث تم تقسيمهم إلى مجموعتين كما تقدم. وقد تم علاج المجموعة الأولى طبقا لبروتوكولات العلاج الخاصة ب (مجموعة أورام الأطفال) التي تعتمد الجراحة علاجا أوليا لهذا المرض ثم يليه العلاج الكيميائي أو العلاج الكيميائي والإشعاعي.

وقد تم مقارنة هذه الحالات بالحالات التي تم علاجها طبقا للمدرسة الأوروبية لعلاج ورم ويلمز وهي تعتمد العلاج الكيميائي علاجا أوليا ثم تليه الجراحة ثم مزيدا من العلاج الكيميائي أو العلاج الكيميائي والإشعاعي.

ودراسة خلصت إلى تقارب نتائج خطى العلاج وهذا واضح أيضا في الدراسات العالمية الأخرى التي تتناول هذا الورم.
العلاج الجراحي الاستباقي لـ (ورم ويلمز) عند الأطفال

رسالة مقدمة من الطبيب: أحمد محمد عبد العزيز الصرورى

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توطئة للحصول على درجة الدكتوراة في جراحة الأورام

تحت إشراف

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